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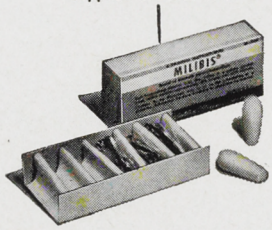

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Medicine

Anticoagulant Therapy*

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In an effort to compare the clinical effectiveness of two anticoagulant drugs, Danilone and Dicumarol, it was necessary for us to review our own clinical material and to cull what information we could from the large literature on the subject. It was felt that a synthesis of our experience coupled with an essence of the literature might be of use, and hence this review.

The clinical material at our disposal consisted of 70 cases which had been treated with Danilone; and 170 cases treated with Dicumarol. A few additional cases received some of the other anticoagulants, but there were not enough in each group to allow proper comparison, except for certain clinical impressions.

The anticoagulants fall into two main groups:

1. Anticoagulants that are effective when given by mouth.

2. Anticoagulants that are effective only when given parenterally.

I. Orally Effective Anticoagulants

Like many other therapeutic agents, the first effective oral anticoagulant was a gift to medicine from another science. Agriculture had noticed that a bleeding disease occurred in cattle who had eaten spoiled sweet clover. This observation was first made in Alberta in 1922, but not much interest appears to have been shown in it until much later, when the disease was again noted, this time in the U.S.A. Link and his associates undertook an investigation of the phenomenon. The story of how they tracked down the responsible substance in the clover, isolated it, studied its properties and synthesized it, is told in a fascinating manner by Link in the Harvey Lectures of 1944. Indeed, there has been little fundamental added to our knowledge of this subject since this work was done. The substance synthesized was called Dicumarol. Its therapeutic possibilities were at once obvious and it was not very long before these possibilities were being exploited. For some time there was only this one drug in the field, but more recently a number of substances more or less related to dicumarol have appeared. It seems likely, however, that the remarks on dicumarol probably are also applicable to these other substances as well.

Chemical Nature

It had been known for many years that in some people salicylates would produce bleeding. There had been, however, a considerable amount of disagreement as to how this was accomplished; whether by lowering the prothrombin level, as did dicumarol, or whether some other method such as blood vessel sensitivity might be responsible. Although salicylates do lower prothrombin, it takes massive doses before the level drops to anything like dangerous level, and it has therefore been felt that usually salicylates do not produce bleeding by their effect on prothrombin levels. However, the close chemical relationship between salicylate and dicumarol was pointed out by Link who indeed early, suggested that perhaps dicumarol worked by being broken down into two molecules of salicylates. This assumption was quickly disproven.

The relationships between the structural chemical formulae of various members of this group of anticoagulants, and between salicylate and also Vitamin K are indicated in Diagram I.

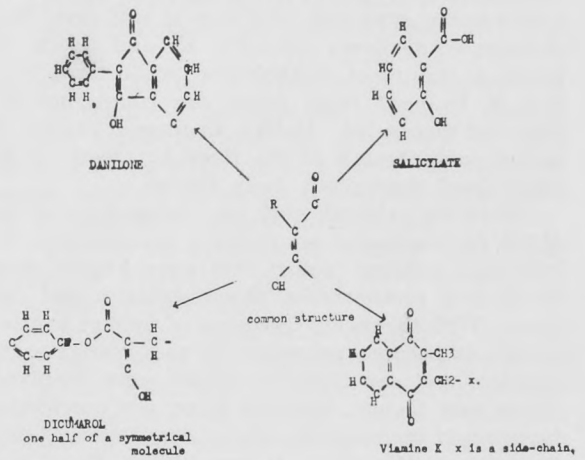

FIGURE I.

Undoubtedly, other orally effective anticoagulants will be found in the future; one recently has been described (Gossypol—found in cottonseed).

Mode of Action

It was soon shown that these anticoagulants did not have any direct effect on blood clotting; that is, when mixed with blood in the test-tube they did not inhibit clotting. It was logical to assume, therefore, that they interfered with the formation of an essential clotting factor, and the fact that they took many hours before any effect was produced was similarly suggestive. The factors

involved in clotting, as they were known at that time, were investigated and it was found that the concentration of prothrombin in the blood decreased when dicumarol was fed. It had been shown that Vitamin K was essential for the synthesis of prothrombin, and that this synthesis occurred in the liver. Because of the similarities in chemical structure of dicumarol and Vitamin K it was suggested that dicumarol might produce its prothrombinopenic effect by competing with Vitamin K in the synthesis of the prothrombin. Jaques showed that dicumarol is rapidly taken up by the liver when this drug is ingested. More direct evidence was also found; in dogs treated with dicumarol perfusion of the liver did not lead to the appearance of prothrombin in the perfused fluid, whereas in untreated animals prothrombin appeared in the perfused fluid. This all suggested that dicumarol owed its anticoagulant effect to inhibition of prothrombin manufacture by the liver. At first it was thought likely that vitamin K was incorporated into prothrombin and that the liver, being unable to distinguish between vitamin K and dicumarol, used dicumarol when it was present instead of the K and therefore formed an inactive prothrombin. However, the inability to demonstrate either vitamin K or dicumarol in prothrombin makes this theory unlikely. It was therefore suggested by Collentine and Quick that vitamin K functions as an apoenzyme involved in prothrombin synthesis, and it is at this level that dicumarol displaces vitamin K and leads to eventual failure of prothrombin production. Vitamin K in very large doses can counteract the effect of dicumarol. Unlike dicumarol vitamin K is not concentrated in the liver but tends to be distributed throughout body tissues.

When the original work was being done on the effect of dicumarol on clothing mechanisms the only four clotting factors that were known were fibrinogen, prothrombin, thromboplastin and calcium. With the recent discovery of further clotting factors it became necessary to re-investigate the problem and see if these factors were involved. These new factors, bye and large, are accelerator factors and increase the rate of conversion of prothrombin to thrombin. It was, indeed, found that the new factors were affected and that convertin was early decreased by dicumarol. Mann found co-thromboplastin activity to be lessened by dicumarol and other workers have also reported various factors as being somewhat decreased early in the course of dicumarol therapy. Fortunately the effect on these factors is not profound, and it is evanescent, persisting only for the first few days of therapy. However, the fact that they are early affected might account in part at least, for the tendency of the prothrombin level, as determined by the usual one-stage method, to drop in an accentuated fashion during the first few days of anticoagulant therapy. (See figure 2).

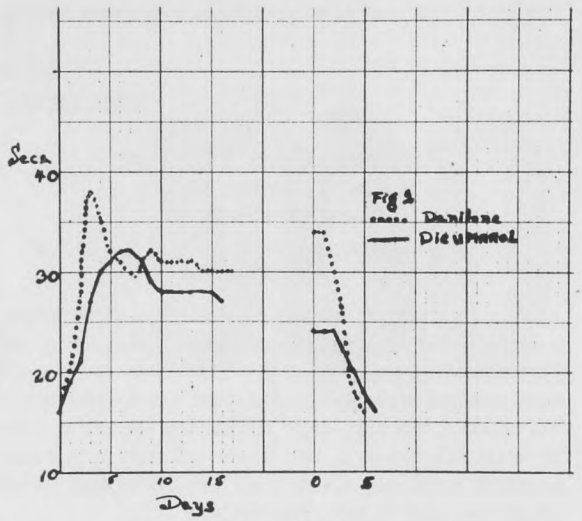

Figure 2

Curves showing the rate of drop in prothrombin time after beginning therapy (average curves of the cases). Note that Danilone effect appears sooner. Note that in both cases there is a tendency for the prothrombin to drop to its lowest point during the early days of therapy.

The latter part of the figure indicates the rate of return to normal after the drug is discontinued. Danilone has a more rapid return to normal. The figure shows also that on the average, prothrombin levels were lower with danilone than with dicumarol at the end of the course of therapy.

While the proof seems to be quite satisfactory that these anticoagulant drugs effect a lowering of plasma prothrombin level, there are observers who are not convinced that this is the mechanism by which these drugs have their therapeutic effect. The clotting time, as determined by usual laboratory methods, is within normal limits, unless very low, indeed dangerously low, prothrombin levels are produced and it is hard to believe that the small change induced could have much effect in inhibition of intravascular clotting. Vascular thrombosis begins as a platelet thrombus, and some have felt that these drugs act by inhibiting the tendency of platelets to adhere to each other and to the vessel walls, and in this manner inhibit thrombus formation. While this may be so, it does not seem likely that it would inhibit the propagation of a thrombus already formed, and therefore one still clings to the antiprothrombin effect as being significant in this regard.

In addition to anticoagulant properties dicumarol has other actions that may play almost insignificant roles in therapeutics; it is a vasodilator; it is mildly antibacterial, it is a mild analgesic. While most of the work has been done with dicumarol, available evidence would strongly suggest that the same conclusions can be applied to other cumarols, and also to the indanedione group, and probably to salicylates as well. Differences in the rate of development and the persistence of action appear to depend on such factors

as solubility, rate of absorption, and time of retention in the liver.

Let us accept the thesis, then, that dicumarol acts by causing depression of prothrombin formation in the liver. Let us assume that this effect is almost immediate after the drug is given, and that it is 80% complete (not a safe assumption, of course). It is then, obvious that the rate of decrease in circulating prothrombin is going to depend on the normal rate of destruction of prothrombin. As the normal survival time for prothrombin appears to be somewhere between 16-48 hours, many hours will have to go before the prothrombin has decreased to therapeutic levels. It is also apparent that this fact sets a limitation on the speed with which any drug in this series can produce effective therapeutic levels of prothrombin.

Metabolism

Comparatively little is known about the pathways by which these drugs are metabolised. It is known that they concentrate in the liver after absorption, and then appear in the plasma. Dicumarol does not appear as such in the urine to an appreciable extent, but its breakdown products do. Danilone does appear in the urine. This drug is colorless in acid solution and intensely orange in alkaline solution, a fact that can be used in estimating its concentration. Using this we have found that on the average, about one-third of the administered dose appears unchanged in the urine. Incidentally, if the pH of urine containing Danilone is near neutrality or is alkaline, it will have an orange-brown color and this has been mistaken, by the uninitiated, for hematuria.

Estimation of plasma levels can be made on a similar basis and if one compares plasma levels of unchanged danilone with the prothrombin time of the same individual, they tend to run parallel. However, in different individuals there is no strong correlationship between the plasma level of danilone and the prothrombin level. Probably the plasma level is an indication of the dose administered rather than an indication of the effect achieved.

These drugs are more soluble in fat solvents, than they are soluble in water and aqueous solvents. One would wonder, therefore, if they did not tend to accumulate in the fat depots. It has been our clinical impression that stout patients require larger doses and took longer to return to normal after discontinuation of the drug than did lean patients.

Theoretical Factors Affecting Activity

Assuming that the above mechanisms are probably the true mechanisms by which these drugs function, then certain theoretical considerations present themselves:

i. Factors affecting absorption of the drugs will be of importance in determining clinical response. As these drugs are more soluble in alkaline than in acid media, the pH of the intestinal contents may be important; as they tend to follow absorption of fat substances the presence of bile and other similar factors instrumental in fat absorption may also be important in the absorption of these drugs. Certainly, the absorption of dicumarol can vary from 0-40% of the administered dose, and the average net absorption is 27% of the administered dose. About one-third of the absorbed dose reappears in the bile and is presumably again partially reabsorbed.

Dietary factors may also enter the picture. Barker felt that patients who were eating a suboptimal diet were more sensitive to these drugs than those on a normal diet. Wright thought that a quart of milk ingested daily tended to stabilize a varying prothrombin time in patients treated with dicumarol; Bramble noted that the patients recovering from lower bowel surgery were more sensitive to dicumarol and thought that they should be given 30-40 mg. of vitamin K daily to stabilize the effect of the drug. Others have not found, however, that dietary factors play a significant part in the response to these drugs. Overman and Link have noted the effects of fasting and dietary vitamin K and C on sensitivity to dicumarol. They could demonstrate some effect, but how important this could be in the average case is uncertain.

Factors influencing the synthesis of vitamin K by bacterial flora of the intestinal tract may also come into the picture. Penicillin, sulfonamides, aureomycin and so forth can inhibit such bacteria and theoretically decrease the available vitamin K, and hence increase the sensitivity of such patients to the effects of dicumarol. Indeed, prolonged uses of powerful antibiotics alone have been blamed for hypoprothrombinemia.

There is no evidence to suggest that these drugs are altered in the gut, with the possible exception of salicylates.

ii. Antagonists other than vitamin K may be involved. Macht has suggested that such drugs as digitalis, xanthines, mercurial diuretics, shorten the clotting time and tend to promote intravascular clotting, even though the prothrombin concentration is not affected by these substances. Whether or not they would tend to oppose the action of the orally effective anticoagulants is not known.

iii. **Synergists.** The level of circulating blood platelets may be a factor in the tendency towards bleeding, and this is more likely to occur with thrombocytopenia than without, even though the prothrombin time is not affected by the decrease in circulating platelets.

Other substances have dicumarol-like activity and can enhance the prothrombinopenic effect of this group of drugs. Thus, salicylates can potentiate the activity of dicumarol, and in comparatively small doses can depress a low plasma

prothrombin to dangerous levels. Alcohol also seems to do so. Heparin does not ordinarily effect the prothrombin time when given alone in the usual therapeutic dose, however, it has been our impression that when heparin and dicumarol are given together there is a more rapid decrease in the apparent prothrombin levels than when dicumarol is given alone.

ACTH and cortisone have some minor effect on the clotting mechanisms of blood which are probably not enough to be of clinical importance when used with these anticoagulants.

iv. **Presence of Liver cell damage.** It might be expected that if liver cell damage were present, an increased sensitivity to these orally effective anticoagulants would be encountered. This has been borne out in animal experiments and in human cases. In the presence of hepatitis, therefore, one must be very cautious in the use of such drugs. However, liver disease not directly involving liver cell function may not show increased sensitivity. Livers with moderate fatty metamorphosis for example, in our experience, did not show such sensitivity, and, indeed, in two cases where this pathological feature could be verified by liver biopsy, marked resistance to the action of dicumarol and danilone was encountered.

v. Disturbed renal function might be expected to increase sensitivity to this group of drugs by decreased excretion in the urine. Comparatively little dicumarol is so excreted however, so that it might be expected that this drug would show little change in its effect in renal disease. This has been borne out in certain observations; Sachs found no increased sensitivity to dicumarol in renal damage; experimental work in animals also did not result in any change in response. As danilone is excreted in the urine as danilone, it is possible that impaired renal function might increase sensitivity to this drug. So far we have not encountered any reports on this matter.

Theoretical Versus Observed Dangers in the Use of Oral Anticoagulants

In the use of a drug undesirable effects can be anticipated because of (1) direct damage inherent in the "poisonous" nature of the drug; (2) overdosage; (3) sensitivity reactions; (4) anomalous reactions.

1. **As a poison.** Because this group of drugs acts by inhibiting the manufacture of prothrombin by the liver, some physicians have simplified its action by calling it a "liver poison" and therefore by a semantic twist, assuming that it can induce liver damage. This possibility has been investigated experimentally, it is found that therapeutic doses do not produce any evidence of liver damage, whereas very large doses may sometimes produce histological changes in the liver which consist of minor degrees of central necrosis. There is no good evidence that this group of drugs can produce any permanent liver damage; nor indeed, damage of other organs.

In our own series of cases, 60 patients came to autopsy; 30 of these died while they were being treated with anticoagulants and 30 died at varying intervals of time since completing their course of anticoagulant therapy. In neither group did we encounter any lesions that could be attributed to the poisonous effects of this group of drugs. Fatty metamorphosis of the liver was encountered in four cases and was no greater than the usual incidence of this finding in post-mortem material. An acute hepatitis was discovered in one case, which was probably an homologous serum hepatitis. He had been treated with danilone, the course being started a few days before death, and he did show increased sensitivity to this drug, as might be expected in the case of liver cell damage. While one could maintain that this hepatitis was produced by the drug, there is no evidence for or against such an assumption.

2. **Overdosage.** The dangers of over-dosage cannot be escaped, and where one is using a drug to decrease the clotting ability of blood, the danger of bleeding from overdosage is inherent in the nature of this drug. It should be pointed out that hemorrhage does not by any means inevitably follow a drop in the plasma prothrombin level to below the therapeutic level. It should also be pointed out that there have been cases where bleeding has occurred where the prothrombin levels are not below the therapeutic level, although this is exceptional.

Dangerous bleeding occurring at therapeutic levels usually has some adequate explanation; presence of a disease where bleeding tends to occur such as in subacute bacterial endocarditis, placing of needles into body cavity while the patient is receiving anticoagulant therapy (spinal puncture, thoracentesis, liver biopsy) or in such procedures as Sympathetic blocks. Bleeding can occur from raw surfaces such as a duodenal ulcer, gastric carcinoma, prostatic punch area, etc., and such circumstances are contra-indications to the use of anticoagulant drugs, either relative or absolute.

As a rule, one does not anticipate bleeding unless the prothrombin level is less than 10% of average normal plasma level.

In our series, one post-mortem disclosed the presence of cardiac tamponade from hemopericardium, following myocardial infarction, and this occurred on the second day of anticoagulant therapy when prothrombin levels were not unduly depressed. Hemopericardium has been mentioned as a complication of anticoagulant therapy in myocardial infarction, and is said to be four times as common in patients so treated as in patients not

receiving anticoagulant therapy.

In no other case, however, was any evidence of bleeding found that could have been contributory to the death of the patient.

The incidence of "bleeding" in various series of reported cases seems to depend on what levels of prothrombin concentration were maintained, as well as on the adequacy of laboratory control of the drug. Those series in which the prothrombin levels were maintained below 20% of normal encountered bleeding in about 10% of cases. In series where the levels were maintained between 20-30% only 2% showed any evidence of major bleeding, and this usually occurred in the genito-urinary tract, and was very rarely fatal.

In our own series of cases clinical bleeding was encountered in five cases; an incidence of about 2%. In one case bleeding occurred from an active duodenal ulcer; the ulcer was known to be present, and the risk of bleeding was taken as a calculated risk. Bleeding occurred when the prothrombin level dropped to 10% and stopped when the level rose to 30%. With consummate daring, the doctor in charge of the case did not discontinue the anticoagulant (tromexane) but everyone watched with considerable anxiety. It would only be under exceptional circumstances that one would be willing to accept this sort of risk.

Hematoma into the thigh occurred in one case when the prothrombin level dropped below 10%.

Three cases of hematuria, one in an ambulant patient, occurred. None of these was worrisome enough to cause any active treatment apart from discontinuing the anticoagulant drug.

We have knowledge of four fatal cases of hemorrhage, and one near-fatal case not included in this series. One fatal case and one near-fatal case occurred in people taking dicumarol on their own initiative without laboratory control, while at home. One followed penetration of a serous cavity and fatal bleeding occurred into this cavity; and the fourth case occurred when danilone was used ten days after a prostatic transurethral resection in a desperately ill patient, and bleeding occurred from the operative site enough to tip the balance in this case.

These cases indicate that there is a risk involved in the use of these drugs and that some intelligence and a lot of good laboratory control must be used with such therapy.

3. **Sensitivity Reactions.** By this we mean reactions allergic in nature, such as the development of urticaria or other such skin reactions; allergic granulocytopenia and so forth. We have not encountered this in our series. In view of the occasional "aspirin" sensitivity, particularly in asthmatic patients, and the close chemical relationship between dicumarol and salicylates, one wonders whether such sensitivity reactions might not occur.

4. **Anomalous Reactions.** Occasionally one encounters anomalous reactions to anticoagulant drugs given orally, in that either more or less of a hypoprothrombinemia than anticipated occurs. We refer to these as hyper-reactors and hypo-reactors.

(a) **Hyper-reactors.** These are patients who show a fall in prothrombin concentration which is greater than should have occurred with the given dose. This reaction occurred in seven of our cases. The most striking one was that of a male with hypertensive cardiovascular disease and a peripheral vascular occlusion. He had an initial prothrombin concentration of 100%; he was given 300 mg dicumarol, then the next day 100 mg and the third day another 100 mg. His prothrombin level on the third day was 60%. No further dicumarol was given. His prothrombin level dropped to less than 10% over the following three days and stayed there for two weeks! He had some microscopic hematuria (included in the cases of hematuria mentioned above) and when he shaved there was some slight oozing of blood from small abrasions but otherwise, nothing untoward happened. He was given oral vitamine K which did not appear to have any effect and spontaneously his prothrombin returned to normal over the third week. He was watched with considerable anxiety, and blood was ready for emergency use, but was not required.

In two other cases where hyper-reaction was evidenced moderate circulatory collapse had occurred following myocardial infarction, and this had persisted for several hours. Perhaps this was responsible for the increased sensitivity (liver anoxia?). No untoward reactions occurred in these patients.

Four additional cases were hyper-reactors, all critically ill, and all were examined at post-mortem. One case had an unexpected carcinoma of the stomach as well as congestive heart failure and uremia; one had a terminal hepatitis (mentioned above), and the other two had myocardial infarcts and no anatomical reason for their hyper-reaction was encountered.

b. **Hypo-reactors.** By this we mean a failure of the prothrombin level to decrease in proportion to the administered dose of anticoagulant. This situation was encountered in two cases as an initial response; it developed after a normal response to varying degrees in 15 further cases.

The most striking ones were those that failed to respond initially, and both were women. One was an obese woman who had a myocardial infarction. She was given an initial dose of 300 mg of dicumarol, and then daily doses of 100 mg, but her prothrombin time remained at 100% for 7 days. She was then given danilone instead, 100

mg daily, and showed a prompt response. Whether this was a case of resistance to dicumarol and sensitivity to danilone or whether the response was fortuitous we cannot say.

The second case was also that of an obese woman, an alcoholic, who froze her limbs. She was resistant to both dicumarol and danilone. A sympathectomy was done, and a liver biopsy taken at that time showed the presence of marked fatty metamorphosis.

The fifteen further cases were ones that responded to usual dosage of anticoagulants, and were maintained satisfactorily on an average daily dose. They gradually showed escape from the effects of the daily dose, and required increasingly larger doses to maintain prothrombin levels within therapeutic range. This occurs more frequently with danilone than with dicumarol. In three of these cases increased resistance coincided with fresh intravascular thrombosis or with clinical evidence of extension of thrombosis, and whether this occurred because the prothrombin levels were returning to normal, or whether the prothrombin levels rose because they were developing intravascular clotting is impossible to say.

We have only encountered the one case that seemed to resist even large doses of anticoagulant.

Wright suspects malignancy when a patient is resistant to anticoagulant therapy. He suspects underlying malignancy, if (1) thrombophlebitis persists or is migratory in spite of adequate anticoagulant therapy in adults over 30; (2) whenever there is unexplained bleeding with prothrombin at therapeutic levels. We were not impressed by the occurrence of this phenomenon in our series.

Laboratory Control

It should be obvious from the above discussions that **adequate** laboratory control is essential if one is safely to use this group of drugs. Indeed absence of such laboratory control is an absolute contraindication to their usage.

The determination of prothrombin time by various modifications of the one-stage Quick method are not difficult, and can be done by any intelligent technician, or even a physician, who will take the time to read up about it, and who will take the trouble to do the test carefully as outlined in the standard texts. Many authors point out that this test is not a specific measure of the prothrombin concentration, but actually is a measure of many clotting factors. However, once the technician is aware of this, the anomalies that may occur are uncommon and can be watched for There are, however, a few points that should be mentioned that are not encountered in most of the laboratory texts.

1. **Method of Expressing Result.** The result can be expressed in terms of the actual number of seconds that are required for the clot to occur in the test. The relationship between actual seconds and prothrombin concentration is not a linear relationship; that is, when it takes twice as many seconds for the clot to occur, that does not mean that there is half as much prothrombin. Because of this fact, and because the potency of the thromboplastin used in the laboratory determination may vary and thus affect the significance of the actual time, in seconds, it is best not to express prothrombin results only in terms of seconds, unless one can always have thromboplastin of the same potency. It has therefore become customary to express prothrombin levels in terms of % of normal. This figure is obtained by construction of curves or tables based on the dilution of pooled normal plasma with pooled normal plasma that has had its prothrombin removed. The normal pool is assumed to have 100% prothrombin concentration. These curves are very reproducible, and different laboratories can develop the same curves, and therefore if the curves are properly constructed and the test properly run, the expression of prothrombin levels in terms of per cent is a very satisfactory method. It is also customary to report, in addition, the actual number of seconds taken for the sample being assayed to clot, and also the actual number of seconds it has taken for a normal control plasma to clot. This furnishes additional control to the physician.

Commercial thromboplastin as put out by the Difco Company has been very satisfactory in our hands, and shows little variation in potency.

2. A common error is allowing the plasma to stand too long before doing the test. This will result in an apparently low prothrombin. Some physicians carry samples around in their cars for many hours and expect to have an accurate prothrombin estimation done on this sample, and this is not possible. Another point is that the blood must be collected in a standard amount of anticoagulant (oxalate). Some physicians do not realize this, and bring in samples that have been collected in unknown amounts of oxalate, and this also makes proper assay impossible.

3. If proper technique has been employed, it is not likely that one will encounter falsely high prothrombin levels; that is, one does not find a sample with very low prothrombin activity giving a near normal prothrombin time. Any false results that are likely to occur (in the absence of poor technique) are likely to be false low results. Occasionally this can be puzzling and once in a while may lead to the denial of a useful drug to a patient. The false low prothrombin to which we are referring is not due to any technical fault, but appears to be due to the presence of an inhibiting substance present in the patient's plasma. This inhibiting substance is very sensitive to dilution; that is, if the plasma is diluted it loses its effect at comparatively low dilutions. This substance

appears only in the early stages of intravascular clotting and is generally gone within a day or so. Presence of antithrombin has also been reported in acute pancreatitis. Because of this fact, we have adopted the following technique:

When a prothrombin determination is received in the laboratory on a patient who is not receiving anticoagulants and this prothrombin is abnormally low when tested, we make a ¼ dilution with saline, and repeat the test on this dilution. The diluted plasma should show a prothrombin per centage somewhere in the region of ¼ of the original prothrombin, if there is no inhibitor. If the prothrombin concentration on dilution is considerably higher than anticipated, then it is assumed that an anti-substance is present. This can be verified by mixing the patient's plasma with normal plasma and seeing if there is inhibition produced. Two cases may illustrate this point:

I. 58-year-old male with history and electrocardiogram evidence of myocardial infarction that morning. Control prothrombin determination showed a time of 5 minutes, which is less than 10% prothrombin. This was repeated on a fresh sample and confirmed. Diluted ¼ it had a prothrombin time of 20 seconds or about 80%. Mixed with normal plasma, it prolonged the clotting time of the normal plasma giving a figure indicating less than 50% prothrombin concentration. He was placed on anticoagulant therapy in spite of the abnormal time, and the following day his prothrombin level was 80% undiluted, and he ran a normal response to the drug.

II. 18-year-old youth with clinically rapidly progressing thrombosis of the veins in his lower limbs and two pulmonary infarcts. His prothrombin concentration was repeatedly assayed at 34-45%, and because of this he was not given anticoagulant therapy. His diluted plasma suggested that his prothrombin was normal and that he had anti-substance present. He died of pulmonary embolism, and at postmortem no underlying cause for this extensive intravascular clotting was found. Possibly in this case, anti-coagulants might have been life-saving.

Choice of Drug

Theoretically, the perfect anticoagulant should have the following characteristics:

1. Effective orally or parenterally.
2. Action should begin promptly and should persist for 6-8 hours only.
3. It should be easily controlled without laboratory test.
4. Rapid neutralization of the anti-coagulant effect should be readily possible.
5. It should be non-toxic.
6. It should be non-sensitizing.

No known drug even begins to approach this perfection.

In so far as the orally effective group is concerned the essential difference between them is in their speed of action and the duration of their activity.

We have had reasonable amount of experience with dicumarol and danilone, and very limited experience with tromexan and cyclocumarol.

Danilone appears to be most satisfactory for hospital use, because it acts more promptly, and its action does not persist for a long period of time, and it is comparatively easy to control. Tromexan acts fairly quickly, but not as rapidly as danilone, and it is more difficult to maintain a steady prothrombin level with this drug. This has been our experience and is borne out when one examines the prothrombin response of cases in the literature. Dicumarol acts more slowly and its effects persist longer, and it is particularly useful for prolonged, and ambulant therapy where a patient may be stabilized by this drug for months, without varying much. Such a stable level is not likely with the shorter acting drugs. Cyclocumarol also has a fairly consistent effect, and may be the drug of choice for prolonged anticoagulant therapy.

The dosage of these drugs is not the same, so for hospital use it is best to select one drug and learn to use it.

Danilone dosage is generally easier to manage than the others, because it is more difficult to produce a profound drop when the dosage is increased by a small amount. By this we mean that if a patient is receiving 75 mg of this drug a day and the dose is increased to 100 mg usually one does not find a marked drop in prothrombin activity. With dicumarol increasing the daily dose from 50-75 mg. per day may produce quite a profound depression of the prothrombin level.

In our experience, patients on danilone tend to "escape" after a while; that is, their prothrombin levels tend to rise towards normal and the dose often must be increased considerably to maintain therapeutic levels.

Some phenylindanes have estrogen activity, but this effect has not been reported, to our knowledge, with danilone.

An oral anti-coagulant that is not used therapeutically, may have some clinical importance; this is one called Warfarin, and it is used as a rodenticide. It is placed in water and the rodent gets repeated doses of this when it drinks and eventually bleeds to death. If children or pets accidentally ingest a single, small dose, it is unlikely to be harmful. However, enough might be accidentally ingested to produce clinical manifestations. One case has been reported where it was taken with suicidal intent—not fatal.

Other substances have been suggested as oral anti-coagulants. Salicylates may function in this

manner. It would be most interesting for someone to try a series of cases on salicylates alone to see if they would have any prophylactic effect in the prevention of intravascular clotting, or of thrombo-embolic phenomenon. This drug might approach closer to the ideal than anything else, if it would have such an effect, without depressing the prothrombin levels greatly.

Tocopherols have been advocated in the prevention of intravascular clotting, but careful analysis has shown that they are useless.

Clinical Applications

In general, these drugs can be of use where there is threatened or actual intravascular clotting, and while there is general agreement on this principle, there is some disagreement as to the extent to which it may be applied.

1. **Treatment of Thrombophlebitis and Phlebothrombosis.** It is accepted widely that the use of anticoagulants is very efficacious here. Pain is relieved quite early in the course of treatment, and in some cases the presence and severity of the discomfort or pain seems to vary inversely with the prothrombin time. The course of the disease is considerably shortened and the complications largely avoided. The general procedure is to introduce clinically effective levels of prothrombin activity (15-25% of prothrombin level) and maintain this until all clinical evidence of the lesion has disappeared and the patient is fully ambulant. This requires about 10-14 days, on the average. Occasionally a recurrence of the thrombotic lesion is seen shortly after the drug is discontinued and in unusual cases it may be necessary to treat the patient for several months, ambulant, or even longer. Of course, one must always look for the underlying causes of thrombophlebitis, and intra-abdominal malignancy has a habit of manifesting itself by peripheral thrombophlebitis.

2. **Prevention of Thromboembolism.** It is also rather generally agreed that the anti-coagulants are very useful in the prevention of thrombo-embolic complications that might be anticipated in (a) Surgical Cases — prevention of post-surgical thromboembolic complications can be largely prevented by intelligent use of anti-coagulants. It takes judgment to decide which cases are more likely to develop such complications and to use the drugs here, rather than indiscriminately. Tests have been used to indicate which patient is more likely to develop such complications (Fibrinogen B determinations, platelet adhesiveness, heparin titration curves, etc.) but none of these has turned out to be of much value so far. Therefore, as so often happens, one must judge on clinical grounds and such things as a family history of thrombo-embolic disease; the occurrence of such complications in previous operations, deliveries, or injuries, obesity, type of surgery and so forth, must be the grounds for their use. As a general principle, one attempts to reduce the prothrombin levels to 25-35% of normal by the second post-operative day, and maintain it there until the patient is fully ambulant. Actually, what prothrombin levels are sufficient to prevent thrombo-embolism have not really been worked out. It was done experimentally in animals and found to require a level below 20%, but the experimental method, which consisted of producing marked damage to the intimal surface of a blood vessel, was a very severe one. Some observers have concluded that levels between 50-70% will prevent most such complications, but further evidence is needed on this point.

Urdan gave dicumarol routinely in all major gynecological operations and maintained prothrombin levels at 30-40% until the patient had been totally ambulant for three days. In 450 cases bleeding occurred seven times and was controlled by vitamin K within 24 hours. One case was resistant to the action of dicumarol (hypo-reactor) and developed phlebothrombosis. In the control group there were 9 non-fatal pulmonary embolisms and 4 fatal ones, whereas there were none in the treated group.

White has suggested that dicumarol may decrease the incidence of post-operative adhesions.

(b) Obstetrical cases: because of the high incidence of postpartum thrombophlebitis these drugs have been suggested as prophylactic agents in this state. Early ambulation has considerably decreased the risk of this complication but it is still encountered and there are patients who cannot be allowed up so early. It was first necessary to determine whether or not using oral anticoagulants would affect the infant by being secreted in the milk. Brambel and Hunter found that the effect on the infant was negligible when dicumarol was used. We have not encountered reports of this nature on danilone or other oral anticoagulants.

Brambel and others treated 3,284 cases routinely with dicumarol, using 3,318 cases as a control group. The prothrombin concentration was maintained between 40-50%. Only two treated cases developed any evidence of thrombophlebitis, and in one case this was so mild as to be dubious. In the control group, 16 cases developed thrombophlebitis. Post-partum hemorrhage occurred in 0.5% of the treated and in 0.4% of the untreated group, which is almost a negligible difference. It would seem likely that again, the judicious selection of cases which might benefit from such prophylaxis would be better than routine use of the drug.

(c) Medical Cases: Thromboembolic disease is very common in congestive heart failure, and as high as 48% of patients at autopsy, who have died in congestive heart failure, have had pulmonary

infarcts. Levinson found that 8% of a control group had clinically apparent pulmonary infarcts and that 5% had fatal pulmonary emboli. In a treated group, on the other hand, dicumarol reduced the incidence to 1% and heparin to 2%.

It would seem that in congestive heart failure where the patient is confined to bed, anticoagulant therapy should be considered.

In occlusive coronary artery disease the use of such drugs has been a much debated problem. It has been considered a positive therapeutic approach by some; others have advocated it as a routine procedure, whereas a further group believe that only under special circumstances need it be used. Once again, clinical judgment is required to intelligently use such drugs to the benefit of the patient.

Halten, in a very well controlled series of cases found that while 36% of the control group died, only 25% of those treated with anti-coagulants died. He used alternate cases as a control group, and this seems to be an acceptable experiment. In the treated group pulmonary emboli occurred in 4% of cases whereas in the control group it was observed in 14%. Wright also ran a well-controlled series and found the mortality of 15% in the treated as opposed to 24% in the control group, and Smith had a comparable result in his cases. It would therefore seem that the intelligent use of anti-coagulants will salvage about 10 patients out of each hundred with a myocardial infarct and it is therefore worthwhile.

The evidence would indicate that the anti-coagulants save this number of patients not by limiting the extent of the infarct, or by increasing the rate of healing, but by preventing the fatal pulmonary emboli which probably originate in the lower limbs while the patient is confined to bed. This complication occurs after the first week and therefore there does not seem to be a great hurry in starting anti-coagulant therapy. Although we have not carefully analyzed our cases, it has been our impression that giving heparin at once while the oral anti-coagulant is slowly becoming effective, has not made much difference. Some series have suggested that there is a slightly lower mortality in the first week in those cases treated with anti-coagulants, but this is not very convincing. Smith et al did not find that heparin in addition to dicumarol made any difference to the mortality rate.

The possibility that anti-coagulants might prevent the development of coronary occlusion at once presents itself. It has been claimed that anti-coagulants are very useful in those cases of coronary insufficiency that develop premonitory symptoms of myocardial infarction (coronary insufficiency); 50% of these cases treated with anti-coagulants did not develop myocardial infarcts. However, it is very difficult to control this observation adequately and it will take some time before one can be assured that this observation is significant.

Possible dangers of anti-coagulant therapy in myocardial infarction have already been mentioned; the greater incidence of hemopericardium, possibility of using it in dissecting aneurysm of the aorta, possible theoretical danger in its use where sub-intimal hemorrhage is the cause of the coronary occlusion.

Russek believes that it is unnecessary to place "good risk" patients on such treatment; good risk patients being those without previous infarcts, no intractable pain, no marked shock, no evidence of congestive heart failure, not diabetic, not obese, no history of thrombo-embolic episodes and no arrhythmias.

As a rule, one maintains the prothrombin levels between 20-40% until the patient is fully ambulant.

Other Uses

These drugs have been used in the treatment of peripheral arterial occlusion by embolus or thrombus; in frostbite, mesenteric artery occlusion, and in occlusions of the retinal vessels; and occlusions of the internal carotid artery.

The Question of Long Term Anti-coagulant Therapy

Whether or not anti-coagulant therapy for an indefinite period would prevent further occlusive disease is an unsettled question. There are reports in the literature that would indicate such a possibility. Our experience has been limited to five cases. Three of these cases were in younger men who had had two, three and three infarcts respectively over a period of five years. The first case was maintained for nine months on dicumarol, while he was ambulant. His dicumarol was then discontinued and four years later he has not had a further infarct. In the other two cases, anti-coagulant therapy was maintained for two years without any further infarcts appearing. It was then discontinued. One man died of a fatal infarct ten days later, and the other, a month later. In two older men who have had recurrent infarction, anti-coagulant therapy has been maintained for two and three years respectively without further infarction occurring. It is, obviously, very difficult to assess the value of this therapy. In a further case a male, 50, had recurrent thromboses in peripheral veins, and intensive investigation failed to reveal any cause for this phenomenon, except that he has a continuously high platelet count, and has been classified as an "essential thrombocythemia." During the first year, each time dicumarol was withdrawn a fresh thrombosis appeared. He has been maintained for two years on continuous dicumarol therapy without further episodes.

When long term anti-coagulant therapy is being used, dicumarol is the drug of choice, although

possibly cyclocumerol might be as good or even better. It is soon found that a certain daily dose of the drug maintains a constant prothrombin level, and eventually prothrombin determinations weekly are sufficient to control dosage. The patient must be cautioned against use of aspirin or other salicylate containing drugs. They must be aware of the potential danger, and report at once, if any evidence of bleeding is encountered. We have not met with any complications of prolonged therapy in our small series.

Clinical Contra-Indications

As a general rule contra-indications are the absence of laboratory control; and those situations where one can anticipate serious bleeding if the clotting mechanism becomes defective. Thus:

1. Bleeding diseases such as hemophilia, purpuras, leukemias, and so forth would interdict the use of such drugs. Subacute bacterial endocarditis also is a contra-indication for its use.

2. Relative contra-indications are: possible bleeding site, such as intestinal or stomach carcinoma; peptic ulceration, ulcerative colitis, and so forth.

3. Menstruation is not a contra-indication. Indeed, during the menstrual period women appear to be more resistant to the action of these drugs. The presence of a lesion such as carcinoma of the uterus would, however, be a relative contra-indication.

Although apparently dicumarol does not easily cross the placental barrier, it can do so and affect the foetus, and the danger of abruptio placentae would make one hesitate about using it during pregnancy.

4. Where bleeding in small amounts may be dangerous or uncontrollable, such as in intracranial lesions, thoracentesis, liver biopsy, spinal puncture, one should not use such drugs.

5. Imminent surgery is a relative contra-indication. Surgical procedures have been carried out without mishap in people under anti-coagulant therapy, but this certainly would not be blithely undertaken.

6. Other relative contra-indications are those circumstances where liver damage is present, possibly in severe renal damage, in shock, in the presence of marked debilitation and malnutrition and if used here, probably best to give oral vitamin K as well.

Treatment of Bleeding While on Anti-coagulants

If bleeding is worrisome, or if because of imminent surgery, or for any other reason it is necessary to bring the prothrombin level back to normal then the anti-coagulant should be discontinued. Transfusions of blood can be given, and some prefer fresh blood, although others have used stored blood effectively.

Vitamin K is given, but must be used in massive doses. One way of giving this is to dissolve 1 gm of Vitamin K_1 oxide in 25 cc of 95% alcohol, mix with 500cc of isotonic saline and give intravenously by drip method. If this method is undesirable, then vitamin K ("Hykinone") can be given intramuscularly 10 mg. at four hourly intervals.

2. The Parenterally Effective Anti-coagulants

Long before orally effective anti-coagulants were in use, Heparin had established for itself, both experimentally and clinically, a place in anti-coagulant therapy. Jorpes has summarized much of the information on this substance in his monograph. Heparin was discovered by a medical student, McLean, in 1916. It can be isolated from most body organs but the liver and the lung are particularly rich in it. The granules of the tissue mast cells and the basophiles contain a substance that is probably heparin or a close relative. Presumably the liberations of these granules into the blood stream is a method of autoheparin administration. It is interesting to note that the mast cells become fewer in number in many people as they age, and there is much speculation as to the function of heparin in body economy and whether or not it tends to prevent development of intravascular clotting.

Chemically, it is a mucoitin-sulfuric acid and is strongly acid in reaction. It functions as an anti-thromboplastin and an anti-thrombin; it inhibits platelet agglutination. In large concentrations it inhibits the plasma tryptase activity. In tissue culture heparin inhibits cell division. It has been claimed that heparin also acts as a vasodilator (Gilbert et al) but Russek et al could not find clinical or electrocardiographic evidence that it increased the coronary circulation in patients with angina of effort.

It has recently been shown that heparin reduces the hyperlipemia that follows ingestion of a fatty meal, and this suggests a possible role in fat metabolism and possibly in the development of atheroma. Danilone and dicumarol do not have this effect, but indeed, seem to increase the hyperlipemia (preliminary experiments).

Heparin itself is inactive, requiring a co-factor present in the plasma before it is active. Heparin is rapidly destroyed in the body. Jaques believes that an enzyme, heparinase, is responsible for this. Little heparin appears in the urine unless excessive blood levels are reached, but inactive degradation products (uroheparin) do.

Because of its mode of action, heparin is effective in decreasing clotting time almost at once. If given intravenously this effect is maximum in about 10 minutes, and the duration of activity depends on the dose administered. 50 mg. will last for about 4 hours, although lesser effects can be detected for up to 12 hours.

In therapeutic doses it has little effect on the prothrombin time.

Factors Affecting Activity

Absorption: If the drug is given intravenously there is no problem in absorption and one can be assured of its effectiveness. If given intramuscularly, however, absorption may be delayed. In shock this delay can be anticipated and Gubbay has indeed found evidence to suggest that such does occur. Therefore, when using heparin in patients suffering from some degree of shock, intravenous therapy would be preferable until they had recovered from their shock.

It was reported that heparin was absorbed from the sublingual region in amounts sufficient for therapeutic use, and this looked like a promising advance in heparin therapy. Unfortunately others have failed to confirm this observation and so it will take some further observation before it is known whether or not this method of administration is effective.

Heparin is not effective when given orally.

Antifactors: The effectiveness of heparin appears to vary inversely with the platelet count; patients with low platelet counts are quite sensitive to its effects whereas in the presence of high platelet count considerable resistance may be encountered.

Side Effects

Overdosage can lead to bleeding, of course, as in the case of other anti-coagulants. However, this is unusual with heparin. Because of the short duration of its activity, bleeding is rarely worrisome.

If given intravenously, thrombosis of the vein into which it is injected often occurs because of the very acid pH of the heparin; an anomalous situation where an anti-coagulant produces local thrombosis by irritation of the vein. For this reason when given intravenously, it has to be diluted to minimize this effect.

Local pain may also be encountered when the heparin is given subcutaneous or intramuscularly. It is claimed that heparin can be used subcutaneously if given with hyaluronidase to increase its rate of absorption, and that there is little pain under such circumstances.

Intramuscular injection of heparin has sometimes resulted in the formation of local hematomas, which is undesirable.

Sensitivity reactions have occurred; anaphylactoid reactions have been reported when heparin has been given, but these are quite rare.

Laboratory Control

The dosage of heparin can be controlled by following the clotting time. The desirable range is between 30-60 minutes, according to some observers. This is best done using venous blood and a Lee-White technique. Others have used capillary tubing and determined the clotting time on fingertip blood. Some observers do not feel that it is necessary to follow the clotting time very carefully, and use heparin on a weight-dosage formula with only occasional clotting times. Others prefer to follow the clotting time more closely, at 6-12 hour intervals and govern the dosage accordingly.

Counteraction of Bleeding

Where bleeding does occur in the presence of heparin therapy, the element of time is much more in favor of the patient than where oral anti-coagulants are being used. As a rule, blood transfusion is sufficient. There are other substances which will neutralize promptly the effect of heparin. Protamine is one of these. Toluidine blue, benzidine and other similar substances will also do so, but here one must be cautious about dosage, as larger amounts of these substances act as anti-coagulants. Therefore, from the practical point of view one relies on blood transfusions and time.

Clinical Applications

The indications are much the same as for the oral anti-coagulants. Where prompt action is urgent, heparin is the drug of choice, and hence can be used where pulmonary embolism has occurred; mesenteric artery occlusion, peripheral arterial occlusion and so forth where one wishes to have immediate reduction of intravascular clotting tendency. As mentioned above, heparin does not seem to be indicated in the treatment of coronary artery occlusion, nor in the prevention of thromboses in patients confined to bed.

Where surgery might be required, but in the meantime anti-coagulant therapy is indicated, heparin is the drug of choice.

Where anti-coagulant therapy is desirable but laboratory prothrombin level control is not available or not trustworthy, heparin is the drug of choice.

Because of its tendency to reduce lipemia by converting larger neutral fat molecules into soluble phospholipids by activating a series of protein reactions, theoretically this drug may be useful in the treatment of fat embolism, but this is in the experimental stages only.

Methods of Administration

1. **Intravenously:** Dissolve in glucose and give by intravenous drip. Should contain 0.2 mg per cc and give 14 mg/hr. on the average. Control rate by means of clotting time.

or

Give 50-150 mg. dissolved in saline intravenously every six hours, making a total of 400 mg. per day.

2. **Intramuscularly:** This can be given in concentrated aqueous (10%) solution. Or it can be given in a menstruum as the sodium salt with vasoconstrictors, 200-400 mg. per day. By this method one can often obtain satisfactory levels with one injection every 24-48 hours.

3. **Subcutaneously,** dissolved in glucose, with added hyaluronidase.

4. Heparin has also been given by continuous intra-arterial drip where a local effect was desirable and systemic effects here were avoided.

Synthetic Heparin-like Substances

Sulfated dextrans have an action similar to that of heparin, and have been used experimentally, in place of heparin. Paritol is another synthetic heparin-like substance. Some people develop a peculiar edema which lasts some 6-10 hours when given this. The use of this group of substances is experimental.

Diagnosis and Treatment of Pheochromocytoma

Bohdan J. Lesack

Pheochromocytoma, known also as chromaffinoma or paraganglioma is a tumor arising from the fully differentated chromophil cells.[1, 2] These cells constitute the normal histological anatomy of the adrenal medulla. The tumor in the vast majority of cases is found here but it may occur wherever such chromophil tissue is located normally as in the sympathetic ganglia and the organ of Zuckerkandl, or ectopically as in the retroperitoneal space. Occasionally the neoplasm is malignant. It develops most commonly between the ages of thirty to sixty, but rarely occurs in children.[3] There is an approximately equal incidence among the sexes.

The symptoms, unlike those of most other neoplastic lesions, are not due to presence of the growth per se but are due to secretion by the cells of the tumor of either epinephrine or norepinephrine or a combination of these substances. Upon this is based the diagnosis of the tumor. Many of the observed phenomena are those produced when the normal adrenal medulla suddenly increases adrenalin output.

The most outstanding feature is hypertension.[4] It is one of two types, sustained or paroxysmal, depending upon whether the secretory activity of the tumor cells is continuous or intermittent. If it is of the latter type, the "attack" which occurs is accompanied by symptoms strongly suggestive of pheochromocytoma. The "attacks" occur infrequently at the outset, incidence gradually increasing until eventually they may occur several times during the day and may last from a few minutes to several hours. The chief complaints are sudden onset of a peculiar surging feeling in chest, great fear and anxiety, dyspnea, headache which is often throbbing and located in occiput or generalized. There may be palpitation, pain in abdomen or chest, nausea and vomiting, pallor and coldness of extremities, and other vasomotor phenomena. The disturbance usually ends in a profuse sweat and a feeling of almost complete exhaustion. These symptoms may arise during sudden effort, emotional disturbance, change in posture, or palpation over renal region during examination.[5, 6, 7]

If hypertension is persistent the diagnosis is more difficult but there are several phenomena which may be observed, and, if present together, may lead to a diagnosis of pheochromocytoma.

One of the most common complaints of the patient is generalized persistent sweating. Peripheral vasomotor phenomena such as unexplained coldness of the hands and feet, bluish red mottled discoloration of the limbs, blanching of the digits, occur in high incidence among patients harboring a pheochrome tumor. Numbness and tingling of the extremities are also common. These findings are rare in either essential or malignant hypertension. Other suggestive symptoms may occur at any time. These include throbbing headaches, lasting for a few minutes or a few hours, tremors, feeling of excitement, abdominal distress or pain, palpitation or severe fatigue.

Physical examination does not as a rule yield a wealth of information. If the blood pressure is not elevated it may be completely negative. If it is elevated that may be the only positive finding at the time. However, several special manipulations quite often provide valuable evidence. In every suspected case of pheochromocytoma the blood pressure should be carefully observed and recorded every minute for five minutes in the recumbent, sitting and standing positions. In patients with sustained hypertension any fall, even though slight, of both systolic and diastolic pressure when the patient assumes the erect position should cause one to suspect the presence of pheochromocytoma, particularly when associated with an increase in pulse rate of more than 20 beats per minute and a normal cold pressor test.[5] This test is an extremely useful diagnostic procedure because such a fall of both systolic and diastolic pressure in the upright position below the levels observed in the horizontal position is most unusual in ordinary hypertensive patients. Rarely, during physical examination is the tumor palpable but the pressure of the searching fingers over the adrenal areas may occasionally precipitate an "attack" when the above mentioned phenomena may be observed. Repeated determinations of the blood pressure over several days may reveal remarkable lability of the blood pressure in the sustained type of hypertension.

With regard to blood pressure changes it is well to discuss the cold pressor test. This test, first described by Hines and Brown (1932) is simple test which should be performed whenever suspicion of the tumor exists.[8] It consists of the immersion of one extremity (most convenient is the hand as far as the wrist) in ice water at 4 deg.

to 5 deg. C. for one minute. The great majority of hypertensives (90%) and a small number of normotensives (15%) respond by an excessive rise in blood pressure (more than 20 mm. systolic and 15 mm. diastolic). On the other hand, a normal response (no rise or less than 20 mm. systolic) is observed in 78% of pheochromocytomas. Because of the possibility of a false positive or a false negative finding this test is useful mainly as a screening procedure and must be corroborated by other tests.

A sustained pyrexia of one degree Fahrenheit or more, if unexplained, should, in the presence of other evidence, suggest pheochromocytoma. It may occur sporadically and bear no relationship to paroxysmal attacks. It is suggested by Smithwick (1950) that in suspected cases a rectal temperature should be taken frequently over a 48-hour period wherever possible because this slight elevation is much less frequently found in essential hypertension.

The usual laboratory investigations are of little value. Special tests, on the other hand, are extremely useful. Since epinephrine causes mobilization of stored glycogen, the fasting blood sugar level is often in excess of 120 mgms. per 100 c.c. In Smithwick's series this finding was present in 64% of pheochromocytomas and in only 13% of patients with essential hypertension. Glycosuria occurs in about 50% of patients with a tumor. The finding is significant if diabetes mellitus can be ruled out. Fertig reports finding proteinuria, cylinduria, and hematuria which he attributes to a pheochromocytoma.[9]

In a significant number of cases the B.M.R. is elevated by twenty per cent or more. In these cases hyperthyroidism must be excluded as a causative factor. The metabolism may fluctuate with adrenalin output and will not respond to antithyroid drugs.

X-ray plates of the abdomen may reveal calcification in the tumor as an opacity above the kidney. If sufficiently large the tumor (even though radiotransparent) may exert pressure on the neighbouring kidney and cause downward displacement and/or distortion of the calyces. An intravenous pyelogram will readily demonstrate this. Perirenal insufflation prior to X-ray used to be performed but this unreliable and dangerous method is no longer employed in diagnosis.

Since the pioneer work of Roth and Kvale[10] with histamine several pharmacological tests have been developed to aid diagnosis of the pheochrome tumor. The agents employed may be divided into two groups.

In the first group are those drugs which produce a sudden rise in the blood pressure with associated phenomena simulating a typical attack. Such substances are most useful in the paroxysmal type of hypertension and are best tried between "attacks." Histamine (0.025 mg.-0.05 mg.) administered intravenously was the first drug to be used in this way. In the presence of a tumor it causes a typical "attack" with a rise in the blood pressure of 100 m.m. in excess of that induced by the cold pressor test. In normals or in patients with essential hypertension the elevation is typically less than that produced by the cold pressor test. The test, unfortunately, is not infallible and many false positive results are obtained.[11]

Mecholyl (metacholine chloride) injected subcutaneously in 10 mg. doses has also been used to precipitate an attack. In the hands of Evans et al (1951) the results with this drug have been excellent, confirming the presence of pheochromocytoma in all of their four cases studied. False positive results were infrequent. Side effects were few and not serious. According to this author Mecholyl is the "best, safest, and simplest screening provocative test for all hypertensive and normotensive patients in whom diagnosis of pheochromocytoma is entertained." [11]

Etamon (tetraethylammonium bromide, TEA) in 300 mg. doses given by vein within a few seconds was found by Evans to be only 50% reliable. The characteristic response is extreme fluctuation of pressure in patients with adrenal tumor. There may also be an associated tachycardia and ventricular arrhythmia. The outstanding advantage of this drug is its relative safety for a dangerous pressor response may be controlled readily by sitting or standing.

The mode of action of these substances is believed to be by direct stimulation of the adrenal medulla, while the action with Mecholyl may also be partially reflex. During administration caution is necessary to prevent severe pressor responses and consequent acute left ventricular failure or hypertensive encephalopathy.[12]

The pressor response must exceed that produced by the cold pressor test before a result may be considered as positive. With these, as with subsequent tests to be mentioned blood pressure readings should be taken every two minutes for at least one-half hour after administration of the drug.

The second group of pharmacological agents consists of the "adrenergic blocking substances," which counteract or block the effects of epinephrine or nor-epinephrine released by the tumor into the blood stream. They are administered to patients with a sustained hypertension and characteristically lower high blood pressure due to pheochromocytoma.

Piperidylmethyl benzodioxane (933 F.) 0.25 mg. per Kg. body weight is administered slowly intravenously over a period of two minutes. In the presence of a biologically active tumor there is a distinct fall of blood pressure which persists for

15 minutes or more. In essential hypertension there is only moderate elevation. This test is reliable. Goldenberg and Aranow[13] report only three false negatives in 59 cases and no known false positives. But side reactions may be severe. Acute rise in blood pressure in essential hypertension has been reported (Entwisle, 1951) and may result in serious cerebrovascular accidents.[14]

Dibenamine (N, N dibenzyl-beta-chlorethylamine hydro-chloride) is administered as a saline infusion over a period not longer than one hour. Evans has found, however, that the decrease in blood pressure is not profound and that a high incidence (37%) of probable false positive results occurred. The especial uses of Dibenamine are that it may be employed as a check on the drugs in the first group and administered during operation if hypertension becomes dangerously excessive.[14, 15, 16]

Constant references have been made throughout this discussion to hypertension because it is from this disease that pheochromocytoma most often must be differentiated. Another condition with which the tumor may be confused is symptomatic paroxysmal hypertension due to eclampsia, tabes dorsalis, aortic regurgitation, lead poisoning, angina pectoris and thalamic tumor. Hyperthyroidism, acute or chronic nephritis, periarteritis nodosa, diabetes mellitus, acute anxiety states, hysteria and migraine may also be simulated.[17, 18, 19]

Since secondary tumor or recurrence is extremely rare, the most effective treatment for pheochromocytoma is to remove it. The dangers of excision are the abrupt development of a hypertensive episode with acute left heart failure during manipulation of the tumor, or postoperative hypotension resembling vasomotor collapse. Either condition may be fatal.[16] Several drugs have been used by surgeons to deal with these complications. Console[20] reports the successful use of Priscoline to control hypertensive attacks during the operation, with complete absence of secondary postoperative hypotension. Spear et al (1948)[15] are of the opinion that Dibenamine by restoring the blood pressure to normal for as long as 24 hours and clearing symptoms for 72 is a useful drug in preoperative preparation of a patient. Bartels and Cattell[21] consider that a hypertensive crisis may be avoided by the use of adrenolytic drugs e.g. Dibenamine, 933 F., during the operation. They recommend a Trendelenberg position to avoid cerebral anoxia should hypotension follow tumor removal. Crowther[22] describes use of 933 F. during hypotension. He feels, however, that the latter may have been unnecessary. Grimson[23, 24] expresses the view that the effect of Dibenamine is long lasting and not reversible even with adrenalin. He recommends another drug, C 7337 (2 (N, para-tolyl-N (m-hydroxyphenol)-aminomethyl)-imidazoline hydrochloride), in preference to others, postoperatively and during the operation. Ravitch,[25] reporting a single case, administered only benzodioxane preoperatively until blood pressure reached normal level. During operation he considers it necessary to ligate veins leaving the tumor before manipulating it, thus preventing release into blood of hypertensive substances.

It is perhaps safe to infer from this great variation of opinion that no method has yet been adequately tested and proven superior to others and that more information on surgical intervention, pre-and postoperative treatment is still forthcoming.

The operative mortality (Console et al) varies from 15 to 37 per cent. There appears to be agreement among the various authors that X-ray treatment is not satisfactory. However, the results obtained with many cases after operation, indicate that once diagnosed, pheochromocytoma should be removed surgically.

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Tularemia—Two Case Reports

J. E. Lamb, M.D.*
Murray H. Campbell, M.D.
V. Marie Storrie, M.D.

Tularemia is a specific infectious disease caused by Pasteurella Tularensis (Bacterium Tularense). In 1912 McCoy and Chapin[1] discovered the organism in ground squirrels in Tulare County, California. The bacterium was first isolated from man in 1914 by Wherry and Lamb[2]. Since then the organism has been found widely distributed in the temperate zones, particularly in North America. The common reservoir of the disease is wild rabbits, where it exists as a natural infection, but the organism has been obtained from other animals and birds, including squirrels, rats, mice, hare, skunk, opossum, woodchuck, muskrat, beavers, mink, swine, sheep, quail and grouse. Insects which transmit the disease include animal ticks and fleas, house fly, deer fly, stable fly and bedbugs.

Transmission to man may occur by:

(1) Contamination through minor abrasion of the skin, or through unbroken skin, while handling diseased animals, or by contact with faeces of infected ticks.

(2) Inoculation through bites of ticks, flies and fleas.

(3) Ingestion of insufficiently cooked infected meat, and rarely of contaminated water.

No record exists of direct transmission from man to man.

The incubation period is one to ten days, averaging three days. The clinical course resembles any acute bacterial infection with a rapid onset of headache, chills and fever with temperature up to 104 degrees. In the first week there is frequently a one to three-day remission with amelioration of symptoms, followed by a return of symptoms and fever. The acute phase lasts one to two weeks, with recurrent sweats, prostration, headache, vomiting and aching back and extremities. Following the acute stage there may be several months of debility. The disease is commonly grouped into several types:

(1) Ulcero-glandular — a papule forms where the bacteria enter the skin, quickly becomes pustular, then sloughs to leave an ulcer with raised edges which heals slowly. The regional lymph nodes enlarge, become tender, and may suppurate. In some cases the regional nodes may be tender for forty-eight hours before the papule appears at the sight of entry[3].

(2) Oculo-glandular—may occur as a unilateral or bilateral conjunctivitis, with enlargement of preauricular, parotid, submaxillary and cervical nodes. Small ulcers form on the conjunctiva.

(3) Glandular—enlargement of regional lymph nodes without a detectable primary lesion.

(4) Tularemic pneumonia.

(5) Typhoidal—with systemic symptoms resembling typhoid fever, often fatal. There is no primary lesion or regional lymph node involvement.

(6) Anginose—lesions on tonsil and oropharynx.

The prognosis is generally good; mortality is approximately 4 per cent. Complications include suppuration of nodes, bronchopneumonia, pleurisy with or without effusion, blindness, septicemia, meningo-encephalitis.

Diagnosis of Tularemia is suggested by the clinical picture and the history of contact with wild rodents. This is assisted by agglutination tests on the specific tularemic antigen with serial dilutions of patient's serum. Antibodies appear about the tenth or twelfth day of the disease. A positive agglutination with a serum dilution of 1:80 is significant. The sera of patients with brucellosis may give a positive reaction, necessitating repeated tests to show a rising titer of the tularemic agglutinations[4]. Definitive diagnosis is made by recovery and culture of P. tularensis from the ulcer, nodes or blood. Direct cultures from human cases are usually unsuccessful. The organism is best isolated by infecting a guinea pig with human material. Guinea pigs are very susceptible and die within a week of inoculation.

In previous years treatments used have included organic arsenicals, immune serums, sulfanamides, penicillin and streptomycin. Chlormycetin was given to one of the patients whose case history is reported herein.

Tularemia has been reported from several provinces in Canada with highest number of cases in Alberta. Wood[5] in December, 1951, summarized seven cases which had been reported in Manitoba up to that date. These occurred chiefly in male adult trappers and showed titers ranging from 1:200 to 1:10,240. Wood reported a survey wherein agglutination tests on Indians in north eastern Manitoba and north western Ontario showed 11.7% positive reactions. The areas reporting positive tests corresponded to those where beaver and muskrat were dying of tularemia, although no clinically ill Indians were found. That report stressed the recognition of widespread occurrence of infection in beaver and muskrat population.

Case I

The patient (W. B.) a white male trapper, aged 38, awakened on the morning of April 15th, 1952, feeling feverish and weak. He was perspiring profusely, had severe aching pains in both legs, and shortly after rising began to vomit. He had previously been well and the past history was irrelevant. The symptoms, except for the weak-

From the Department of Medicine, Winnipeg General Hospital.

* Deceased.

† Generously provided by Parke, Davis & Co.

ness, gradually improved during the next thirty-six hours. On the evening of April 16th he noticed soreness in the left axilla and at the left elbow. The next morning the tip of the left index finger was sore and red. Red streaks appeared on the forearm. The weakness became worse and a few days later he saw his physician. Because he had recently been engaged in skinning muskrats in an area where rodents have been known to be infected with the disease, a tentative diagnosis of tularemia was made. He was given penicillin for several days. Improvement was gradual and definite but there was no dramatic change on this antibiotic. By May 15th, when he was sent to the Winnipeg General Hospital for confirmation of the diagnosis and further treatment, he had lost fifteen pounds in weight. On admission to hospital, the patient was found to have ten or twelve pink maculo-papular areas up to 0.5 cm. in diameter on the arm and back. The left epitrochlear node was easily palpable, measuring about 3 cm. in diameter, and a node about 1.5 cm. in diameter was felt in the anterior axilla. The lateral aspect of the nail bed of the first left finger showed a resolving paronychia, with a shallow healing ulcer about 0.5 cm. in diameter. The spleen was not palpable, there were no signs in the lungs and the X-ray of the chest was normal. The temperature was 99.2 and the sedimentation rate was 41 mm. (200 mm. tube). The total leucocyte count was 11,700, mature polymorphs 62, immature 9, lymphocytes 29, hemoglobin was 87% and R.B.C. 4,700,000, with a normal smear. On May 10th, 1952, blood agglutinations for typhoid, paratyphoid and undulant fever were negative. At the same time the agglutination test for tularemia was positive, to a dilution of 1:1000. A blood culture for Pitularensis was negative. During a twelve day period, thirty-six grams of chloromycetin† were administered. He made satisfactory progress on this drug. The patient was discharged May 26th at which time the nodes were not palpable and the finger appeared normal. The sedimentation rate remained at 30 mm. During the stay in hospital the temperature was usually normal with occasional readings at 99 degrees.

On discharge the titer for tularemia was 1:640. The patient was seen July 2nd and the titer was 1:320 with those for B. Suis, B. melitensis and B. abortus again being negative. The patient was perfectly well. Further tests were done on August 27th when a bone marrow culture was negative, and the titer had fallen to 1:160. On November 21st the titer was 1:80 and a complete physical examination was normal.

Case 2

This patient (P. G.) a white male, aged 38, who was engaged with W. B. in skinning muskrats, scratched his finger about April 11th, 1952. On April 17th, two days after W. B. became ill, P. G. felt feverish, nauseated and had general malaise. The scratched finger became inflamed and he developed a sore lump under his arm. He stopped work for a few days but was able to resume his usual activities April 30th. This man was examined at his home on May 28th. He was continuing to feel weak, but was able to do farm chores. Examination showed a flushed, perspiring male, with a temperature of 99.4. The throat was slightly injected. Chest and abdomen and limbs were normal except for excess perspiration. No lymph nodes or spleen were palpable. Blood taken on May 28th, 1952, showed a positive titer for tularemia in a dilution of 1:160; it was negative for typhoid, paratyphoid and undulant fever. On August 27th the titer was 1:160 and the bone marrow culture was negative. By December 4th (when he was in hospital for treatment of a bullet wound in the hand) the titer had fallen to 1:40.

Discussion

Since the causative organism was not recovered from the blood or the skin lesions, differential diagnoses must be considered. These include undulant fever, and septicemia or toxemia complicating a paronychia caused by an ordinary coccal infection. The former is ruled out by repeated negative agglutination tests. It is more difficult to dismiss the latter possibility in individuals who, because of their occupation, might have had a residual positive titer from previous subclinical tularemic infection. It is suggested that the progressive drop in the titer during a six-month period following episodes typical of the ulceroglandular type of tularemia is strong presumptive evidence that the illness was an acute attack of clinical tularemia. Furthermore, the fact that in the first case there was soreness in the axilla before the paronychia manifested itself, is helpful in making a diagnosis of acute infection due to P. tularensis[3].

Summary

Tularemia in human beings has been briefly reviewed. One probable and one possible case have been reported.

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Familial Periodic Paralysis

Dr. Gemmell showed two men—a father and son—who suffer from this strange malady. The father, now 42, had his first attack at the age of 13. The son, now 15, had his first attack at the same age, and so also did a brother of the father. Of the father's family only two developed the ailment, and so far only one of the seven children of the second generation has shown it.

These persons know for some time before hand that an attack is coming but they do not show, at least not in marked degree, the classical prodromal symptoms — excessive hunger, excessive thirst, sweating, vomiting, diarrhoea, pain in the legs.

They are, however, typical in the time of onset —early in the morning, before waking. Then they come to consciousness damp or bathed in sweat and with more or less complete paralysis of all four limbs. Should they waken in the earliest stage of the myoplegia it is to find their legs weak and useless. The paralysis ascends gradually until, after about an hour, it reaches its maximum. Here it remains for hours, or even for as long as two days, and then gradually recedes.

Certain muscles escape. The diaphragm alone maintains respiration. The muscles concerned with the organs of speech and vision are spared, and so are those of the face and throat. Consciousness is not altered and the patient lies immobile and flaccid but completely aware during the hours that the myoplegia persists.

The march of incapacitation is not always slow. It may be cataplectic in its swiftness. Dr. Charles Hunter, in the subsequent discussion, told of two cases that had come under his care. In one, a golfer had driven ball after ball into a stream and quickly lost all power. The other patient was seized with equal celerity when he found upon his hook a fish of the size that almost always gets away. Dr. Hunter did not say whether or not the fisherman had been able to recover his trophy but, if the captive escaped, its captor must have suffered the tortures of Tantalus! Diurnal attacks while unusual are scarcely to be called rare; and when they occur are less severe than those that come while asleep. Moreover, as in the case of Dr. Gemmell's senior patient, the attacks tend to mitigate in severity and to lessen in frequency as the patient grows older.

As in the two cases presented, the condition usually manifests itself about puberty. The younger patient was the eldest of seven children. When asked if any others were affected the father replied that "they were not yet old enough." But while onset at puberty is usual it is not invariable, for symptoms have appeared as early as the fourth year and as late as the sixtieth.

Nor is the disorder confined to men although males suffer more frequently (in the ratio of two to one). I was reminded of a case mentioned by Kinnier Wilson in which a young woman became myoplegic on her bridal night. Such an incident begs for levity. "He led her to the nuptial bower, all blushing like the morn." Then she turned her limpid eyes upon him (or so I presume), murmuring "Big boy, you paralyze me!" And immediately proved her veracity!

The disorder is a most peculiar one, so variable is it in the frequency, duration, and severity of the attacks and also in the distribution of the paralysis. The boy's history revealed that there had been periods when for days on end he would waken myoplegic. And then for days, or weeks or months he would remain normal. So had it been with the father. So was it in many of the reported cases.

Again, the attacks may be of brief duration, a mere passing weakness; or the immobility may sweep rather than creep upwards. Ordinarily there is no danger to life, but should the process involve the diaphragm or the muscles of the throat, as it has been known to do, death may follow.

The mystery of the disease is heightened by the distribution of the myoplegia. Ordinarily it spreads evenly over the body but it may stop at the waist. Or it may involve only the upper half of the body, or it may be hemiplegic in distribution. Indeed, it may confine itself to a single limb and even to a single finger. And in one most peculiar case the patient developed "toe-drop" on one side and "heel-drop" on the other. It is difficult to find any theory that will explain such bizarre behaviour.

Moreover the process does not confine itself to somatic musculature but has visceral expressions as well. Sensation is not affected and the sphincters are spared but thirst, bulimia, anorexia, flatulence, vomiting, diarrhoea have been frequent even to the point of being unusual. The heart is not spared. Its beat is slow and the cardiogram is that of hypo-potassemia. Breathing is shallow and cough is ineffective. Sweating, more or less profuse, is the rule.

What explanations have been offered to account for these curious phenomena? The condition is hereditary and can be transmitted to sons or daughters, by fathers or mothers. An inherited defect of the muscular or neuro-muscular apparatus is likely present. It appears at a time of special endocrine activity and this suggests glandular involvement. Further support is given by occurrence of myoplegia in association with thyrotoxicosis. A search has been made for the cause in some disorder of metabolism. That such a disorder is present is proven by the facts that excess of carbohydrate in the diet, or the adminis-

tration of insulin, or an injection of adrenalin will, any of them, precipitate an attack, all of which lower the blood potassium. But this is not an invariable rule. Dr. Gemmell could not by these measures provoke myoplegia in the younger patient and did not try in the older one.

Again, while a decrease in blood potassium is usual, it is not invariable; nor is the administration of a potassium salt always as dramatic in its effect as it was when given by Dr. Gemmell to this boy. Then, in a matter of minutes, the symptoms abated and within an hour he was able to walk.

The father had found that hard work reduced the frequency of his attacks and that, if he had sufficient warning, he could "walk off" an attack just beginning. Yet this beneficial reaction to effort is not always produced. Some have found exertion to have a contrary effect and have improved themselves by lessening their activity. It is a disorder of paradoxes.

Emotion also may be a provocative agent. The myoplegic bride, the baffled golfer (was he a Scot?) the exultant angler, all were literally overcome by their excitement.

Inasmuch as no single theory can explain all the phenomena of the disorder it is likely that more than one factor is involved. Of these factors the potassium imbalance is specially important for there is no doubt that in some way potassium is withdrawn from the serum and accumulated in the tissues. The administration of 80 meq of potassium salt restored the boy to normal health. Yet Dr. Gemmell said that potassium given orally as a prophylactic failed in its purpose. The discussion that followed was very largely biochemical.

Familial periodic paralysis is so rare as to be readily recognized, for students love to store their memories with the unlikely and unusual. But few diseases are so baffling in their behaviour and, as the curious is more interesting than the common, this case (the father was not under treatment) has been covered more fully than its importance might claim.

Anaesthesiology

A Compatible Solution for the Administration of Blood, D. F. Buschle and M. Saklad, Anaesthesiology, 14 Jan., 1953, 53.

The addition of 5 per cent glucose in water to blood may cause certain bizarre transfusion reactions due to clumping of the blood. Several such reports have appeared in the recent literature.

The addition of isotonic solutions of saline to blood will not cause clumping but has the disadvantage of overloading the patient with saline. It has been shown that, postoperatively there is a retention of sodium which follows adrenal stimulation, and a suppression of urine formation due to release of the anti-diuretic hormone from the pituitary.

The authors, after testing several different solutions for their clumping effects with blood, have found that 5 per cent glucose in 0.09 per cent saline is completely safe, and when it is felt that blood being given to a patient requires dilution, then this solution should be used as the diluent.

M. Minuck, M.D.

* * *

Tetraethylthiuram Disulfide (Antabuse) and the Anaesthetic Agents, B. M. Cooper and C. R. Allen, Anaesthesiology, 14 Jan., 1953, 29.

"If patients who are receiving Antabuse are given small doses of ethyl alcohol they exhibit severe symptoms of acute distress." An occasional death has been reported. "Chemical examination of the blood during the period of distress shows a marked increase in the acetaldehyde content. The physiologic disturbance in these individuals is believed due to this substance."

Rabbits treated with tetraethylthiuram disulphide were given periods of anaesthesia during which the blood levels of acetaldehyde were determined. The anaesthetic agents used were nitrous oxide, cyclopropane, Sodium pentothal, procaine, ether, chloroform and avertin. With none of these agents was the blood level of acetaldehyde significantly altered. Controlled experiments with alcohol showed a marked increase every time.

From these experiments we may conclude that any of the commonly used anaesthetic agents, aside from intravenous alcohol, may be used with relative safety for patients who are being treated with Antabuse. Intravenous glucose with ascorbic acid, and high flows of oxygen will diminish any mild reactions, should these occur.

M. Minuck, M.D.

Influenza

The Department of National Health and Welfare at Ottawa has been keeping the Manitoba Department of Health and Public Welfare informed as to the spread of influenza on this continent. The radio informs us that a mild epidemic has been widespread in France. We are told that the disease is prevalent in the middle western United States (Minnesota for one). The disease in the United States has been identified as of the A prime type.

A telegram from Ottawa dated January 24th states that influenza has broken out in Newfoundland and some cases in Eastern Canada.

We in the Department would ask you to be on watch for typical influenza and report it to us by card, letter or telephone. Dr. Leyton, Director of Laboratories, is anxious to obtain throat and nose washings from a few typical cases so that the type of virus may be identified. Please contact him direct for specimen containers and instructions.

It is to be hoped that we do not have an epidemic but being forewarned may be of value in treatment.

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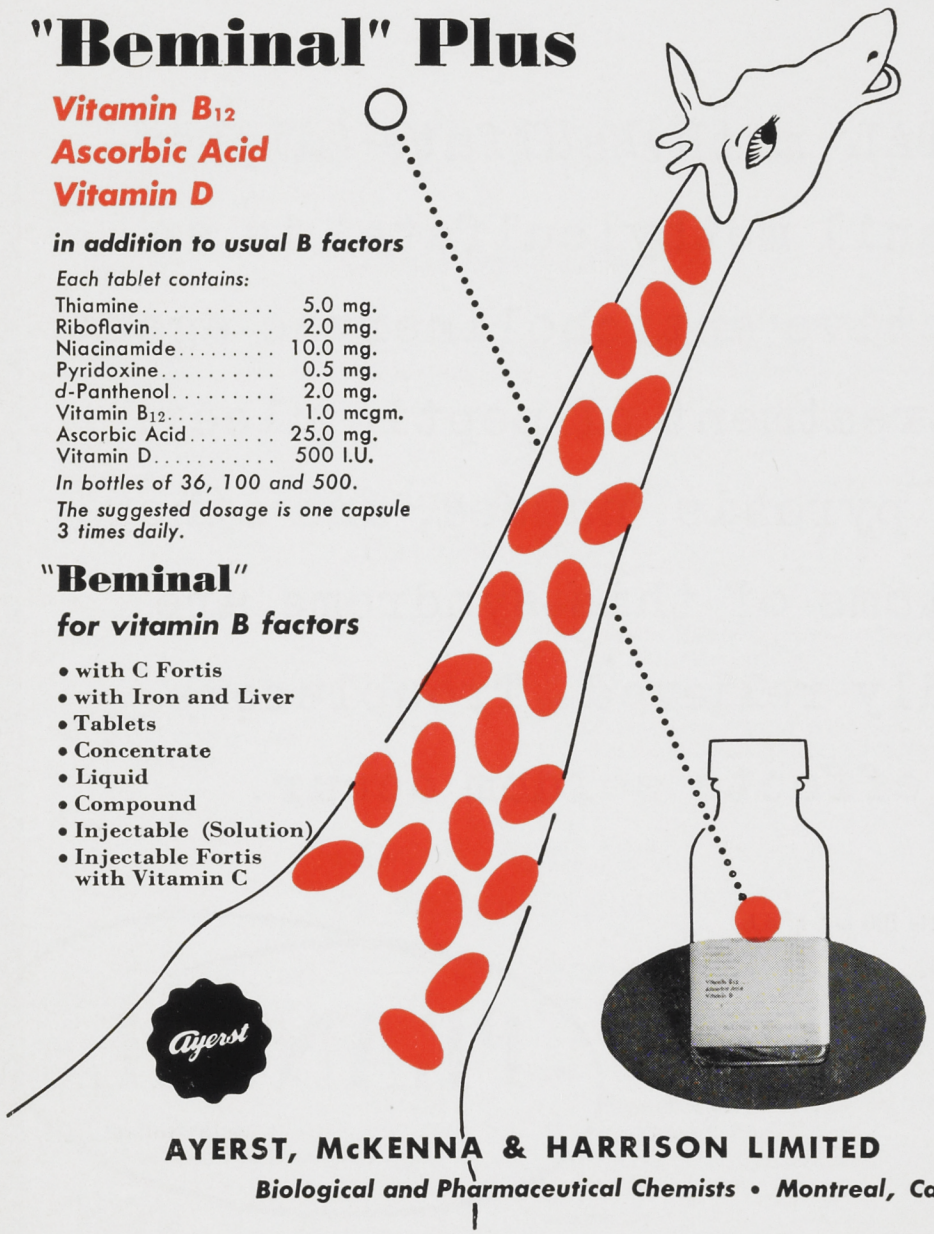

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TENTATIVE PROGRAM

Guest Speakers

Dr. R. R. DeAlvarez,
Professor of Obstetrics and Gynaecology, University of Washington.

Dr. J. F. McCreary,
Professor of Pediatrics, University of British Columbia.

Dr. Hugh Morgan,
Professor of Medicine, Vanderbilt University.

Monday, April 13th

Fort Garry Hotel

Noon

12.00 **Luncheon:**
Speaker: Hon. F. C. Bell, Minister of Health and Public Welfare.

Afternoon

2.00 **Senile Heart Disease — Commonly Mistaken as Arteriosclerosis,**
Dr. Hugh Morgan.

3.00 **Surgical Panel:**
Carcinoma of the Stomach,
Dr. M. R. McCharles, Chairman.

Tuesday, April 14th

St. Boniface Hospital

Morning

9.00 **X-ray Conference,**
Dr. D. Wheeler.

9.30 **Psychiatric Reactions of Pregnancy,**
Dr. J. Matas.

10.00 **Skin Incisions,**
Dr. C. E. Corrigan.

10.30 **Intermission.**

10.45 **Conservative Treatment of Diabetic Gangrene,**
Dr. A. Hollenberg.

11.15 **Infectious Hepatitis,**
Dr. Paul Green.

Noon

12.00 **Luncheon:**
The Abnormalities of Menstruation,
Dr. R. R. DeAlvarez.

Afternoon

2.00 **Spinal Cord Tumors,**
Dr. Hugh Cameron.

3.00 **Panel:**
Hypertension — Diagnosis, Prognosis and Treatment,
Dr. L. G. Bell, Chairman.

Evening

Winnipeg Medical, Theatre A, Broadway

Broadway Buildings:
Chemotherapy of Bacterial Infections,
Dr. Hugh Morgan.

Wednesday, April 15th

Winnipeg General Hospital

Morning

9.00 Department of Surgery:
Dr. C. W. Burns, Chairman.
Acute Urinary Retention,
Dr. C. B. Stewart.
Miller-Abbott Intubation,
Dr. L. C. Bartlett.
Pentothal Sodium Anaesthesia,
Dr. D. M. Huggins.
Difficulties in Diagnosis of Bronchogenic Carcinoma,
Dr. M. B. Perrin.
Public Ward Staff:
Massive Gastric Haemorrhage.

10.30 Medical Ward Rounds:
Presentation of Cases,
Dr. L. G. Bell, Chairman.

Noon

12.00 Luncheon:
Speaker to be announced.

Afternoon

2.00 Indications for Cesarean Section,
Dr. R. R. DeAlvarez.

3.00 Panel:
Vaginal Discharge,
Dr. W. J. McCord, Chairman.

Thursday, April 16th

Children's Hospital

Morning

9.00 Panel—to be announced.
10.00 Rh Factor in Mother and Child,
Dr. B. Chown.
10.20 Hazards of Biochemistry,
Dr. S. Israels.
11.00 Ward Rounds.

Noon

12.00 Luncheon:
Simplified Infant Feeding,
Dr. J. F. McCreary.

Afternoon

2.00 Squint in Children,
Dr. W. Guest.

3.00 Panel:
Rehabilitation of the Handicapped Child,
Dr. J. K. Martin, Chairman.

5.00 Dinner: Fort Garry Hotel,
Speaker: Dr. J. D. Adamson.

Friday, April 17th

Deer Lodge Hospital

Morning

9.00 Symposium on Physical Medicine:
Dr. J. D. Adamson, Chairman.
Methods in:
(a) Hemiplegia
(b) Bronchiectasis
(c) Post-operative Patients
(d) Orthopedic Patients.

Noon

12.00 Luncheon:
Speaker to be announced.

Afternoon

2.00 Prenatal Pediatrics,
Dr. J. F. McCreary.

3.00 Panel:
Management of Fractures,
Dr. G. Ryan, Chairman.

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Editorial

J. C. Hossack, M.D., C.M. (Man.), Editor

Training for Old Age

The fact that an ever increasing number of people are living longer makes old age more important than it used to be. Cicero was in his fifties when he wrote "De Senectute," rather young, one might say, to undertake such a work. But in his time the average life-span was only twenty-three years; anyone who had doubled that span might be considered well qualified to write upon old age.

It took a long time for life expectancy to rise appreciably. A century ago it was still only forty years. In the next half century it had risen only seven years. But by 1930 it was sixty years and today anyone who can reach the age of thirty (as most people do) can be almost certain of exceeding the biblical three score years and ten.

But the end is not yet. The life-span of the lower animals is seven times their age at maturity. Taking seventeen-plus as the age for man, his natural life-span would be one hundred and twenty. Science, which is quite impersonal, will continue to make likely longer and longer lives. The possibility of most men stretching their lives beyond the century mark, the fact that the population of a country doubles every fifty years, the fact, also, that on this continent the over-sixty-five group has quadrupled in the last half-century—all these raise most perplexing problems.

But a world crammed with centenarians is not yet in sight while a country with fifteen per cent of its inhabitants sixty-five or older is almost here. It is not a matter of concern how the billions of tomorrow are to be fed. Some way will doubtless be found. Of much more immediate importance is: what is to be done about old age?

So far, emphasis has been laid on the purely physical aspects of the problem. Social security measures assure shelter, food and clothing for the aged. Medical science with its present active interest in geriatrics is making old age more certain, more comfortable, more free from disabilities. In the matter of material and physical well-being the possible has already been done and the hitherto impossible is being accomplished.

All this leaves only the mind to be considered. Only the mind—as if that were of no importance. The mind that outlasts the body; whose workings make old age a boon for one, a bane for another. Unless to safety and comfort of body can be added peace and contentment of mind, our gift of longevity is not a gift at all but a punishment; the penalty that one must pay for daring to live so long.

It is universally recognized that the capacity for physical work in a man of seventy is no more than half this capacity at thirty-five. But it is not so generally appreciated that other things being equal, the capacity for intellectual effort is as great at seventy as at a much younger age when minds have been kept nimble by continued practice. If the brain is healthy the old man can think as clearly as ever and he is likely to be much more dispassionate and logical in his reasoning. The chief problem of senescence is therefore not physical care, (which needs no lengthy preparation) but how to take advantage of the fact that the brain does not age with the body.

What are the bug-bears of old age? What is the reason for that ambivalence which leads one to desire what he fears and to fear what he desires? The threat of diseases such as cancer, stroke and so on? Perhaps. But not many people dread old age on that account. Much more potent is the shadow of loneliness; the threat of dependence; the menace of long, tedious, unfilled days as useless hour follows useless hour; the feeling of being not only unwanted but of being resented. These are the things that rob declining years of the pleasures they should hold.

More and more people are living longer and longer. Longevity is assured to the majority of children. Old age must therefore become as welcome as the Saturday and Sunday break in the working week. Otherwise one will feel that his journey leads but to a prison. As old age is a state all must anticipate, it is a state for which all should prepare.

And how is this to be done? Let us enumerate again those things which make it unwelcome. First is the fear of loneliness; second, the fear of becoming dependent; third, the fear of uselessness; fourth, the fear of being unwanted. While all old people experience in some degree or other all these fears, not all old people react in the same way. Some are gloomy and pessimistic and wait upon the judgment. Others are alert, cheerful and busy. Whether one accepts the present, and looks upon the future, with pleasure or despair, depends almost altogether on his inner resources. "Men," wrote Cicero, "who have no resources in themselves for securing a good and happy life find every age burdensome. But those who look for all happiness from within can never think anything bad which nature makes inevitable." And Plato, who antedated Cicero and died at the age of eighty-three wrote: "He who is of a calm and happy nature will hardly feel the pressure of age."

That "calm and happy nature" is not something that comes by accident. It is the natural and logical result of happy childhood. The child is father to the man, and as the child behaves so is the man likely to behave. It is not easy to see the gray beard in the toddler but it is not difficult to see the toddler in the gray beard.

Because the achievement of emotional maturity is of such tremendous importance to the individual, and because emotional development is greatest in the early years of life, the child psychologist is of at least equal importance with the pediatrician. The latter assists the parents to assure the healthy physical maturity of their child. In like fashion the child psychologist can help them to bring their child to healthy emotional maturity.

A good deal of disappointment in later life could be avoided by determining early in life the calling, profession or trade for which the child is best fitted, and therefore the one in which the adult is likeliest to succeed. Chance more often than choice is the determining factor in the selection of a vocation. Moreover, when choice has been deliberate it does not follow that success will be the result. Not natural fitness but some quite extraneous factor may have led to an unwise decision. The young person will, beyond question, reveal wherein his strength lies, but he is not always, perhaps is not often, capable of choosing his proper life-work. A youth who is interested in music—a profession in which it is notoriously difficult to excel—is wiser to follow it as an avocation than as a profession, especially if he has qualities that fit him for a less competitive occupation.

But, because a first choice has been relegated to the position of an avocation, its value is in no way lessened. Indeed, it is enhanced, for if one wishes to enjoy life at any age he must have a pleasant and relaxing interest. Avocations are life savers. They should be begun early in life, especially if technical dexterity is necessary as it is playing an instrument, drawing, painting, handicrafts and the like. By the time retirement is necessary or desired there will be the comfort of amusement, and leisure hours can be passed in the creation of objects or sounds which will not only evoke the appreciation of those who see or hear but will enhance the pleasure of him who executes.

Almost without exception the miserable oldster is without such means of expression and relief. He has kept his nose to the grindstone for so long that he feels uncomfortable in the absence of this abrasive. He has never learned to play and is at a loss how to amuse himself. "Sweet recreation ban'd, what doth ensue, But moody and dull melancholy." And in their own fashion women suffer equally with the men.

The past is too much with them, late and soon. They continue their journey with their heads looking over their shoulders, bumping and bruising themselves against the obstacles of the present and dragging from day to day a lengthening chain. Unhappy old men, unhappy old women, who live (if it can be called living) regretful of the past, neglectful of the present, fearful of the future. Considering that in many cases much of this could be prevented is it not logical to attempt its prevention?

It is important that boys and girls should be taught the arts and crafts necessary for their proper training, but it is of equal importance that they should be encouraged to learn those things which alone will be of value in their declining years and which will brighten and lighten their middle age as well.

By far the best avocations are the creative ones. But there are others which require no special technical dexterity. Acquisitiveness can be turned to account. Some get great pleasure in adding stamp to stamp until they have thousands. Others go in for accumulating money in various forms—not the kind in daily use but the currency of other countries and other times. A handful of paper money gives one, vicariously, a sense of tremendous wealth for a few real dollars will purchase hundreds of thousands of millions of marks, or pengoes or drachmas.

Coins hold a greater interest. One looks at a lepton—"the widow's mite"—of which a hundred and sixteen had the value of only one penny; or at an as of Augustus Caesar, the penny of the New Testament; or at a sestertius bearing the effigy of Domitian; or at an obolus which has upon it the head and superscription of Philip of Macedonia—that same Philip against whom Demosthenes thundered and who begot Alexander surnamed "the Great," and which came from the mint twenty-five hundred years ago.

Objects such as these take one far back in history and stir the imagination. One holds in his hand a little Egyptian statuette which first saw the light of day when the Romans and even the Greeks were still barbarians, and six hundred years had yet to pass before the birth of Solomon. Through how many hands have these things passed? For what purposes, honest and dishonest, were they used? Whose dead hands clutched them in their tombs? A sestertius stamped with the effigy of that Antonine whom Galen attended raises the question: did it by any chance linger with him awhile?

Then there are books which have the magic of bearing one through space and time to any land in any age. In books, as in music, one finds

something suitable to every occasion and to every mood. The advantage of gathering much from them in youth is that so much stays unbidden in the memory. "One fond remembrance wakened in the breast, and memory's magic lets in all the rest."

If early reading, however, is to be of ultimate usefulness it must of necessity be purposeful. To read merely to pass time is a waste of both time and opportunity. On the other hand to read with the object of understanding an age or an activity affords lasting profit and pleasure.

Whatever other amusements and interests a person may have, one should be of such a sort that he can do it by himself at any season. And it should be commenced early for it is difficult to teach an old dog new tricks.

Here, then, is the essence of the matter. Guidance during childhood; direction in the choice of vocation; the early cultivation of an avocation, and, when age has come, the frequent and intimate association with contemporaries.

It is proper that people should take an interest in the crippled and afflicted. But it is equally proper that they should fit themselves to enjoy the old age which they are almost certain to experience. Wise people will prepare themselves, and good parents will prepare their children, for this state which nature and science have made almost inevitable, and which medical science is rapidly making more tolerable. A physically comfortable old age is becoming more and more a probability for everyone; and satisfaction and contentment are capable of achievement. Old age can be the golden age of life, and would be if people were trained for it. Then would they look forward to it with enthusiasm saying: "The best is yet to be, the last of life, for which the first was made."

Obituary

Isabel McTavish

Dr. Isabel McTavish, who spent many years in China, died on January 24th in Winnipeg at the age of 70.

She graduated from Manitoba Medical College in 1915 and shortly afterwards began her life work as a medical missioner under the auspices of the United Church of Canada.

The practice of medicine is seldom a sinecure but never is it harder than when to the cure of bodies is added the cure of souls. Few can support this double burden for a long lifetime. Those who do must surely be ranked among the noblest of our calling. It requires a higher than ordinary degree of courage and devotion to turn one's back upon home and friends in order to bring comfort and enlightment to stronge peoples in distant lands. But heroism is in her family for her brother, Dr. Boyd McTavish has the unique distinction of having won the Military Cross on three separate occasions.

Dr. Isabel McTavish was herself decorated by the Chinese Government for her work as Director of Medical Relief during the famine of 1920; for the war in which she was engaged for so long was not only against disease. It was also against poverty and hunger and ignorance. Nor was the battle field always a metaphorical one, for she saw at first hand the atrocities of communists, and during three years worked under the fire of Japanese artillery.

Not only did she practice her double profession, she taught also and organized. She collaborated in the establishment of Cheeloo University and was active in the formation of the Honan Synod of her church. Training schools for nurses were among her accomplishments. In her different capacities she has been responsible, wholly or in part, for the training of many hundreds of young men and women who, as doctors or nurses or converts, keep her influence alive and active.

The message of a missioner is greatly strengthened by his or her own experiences; and, as she went about her beneficent work, Dr. McTavish must many times have had a vivid appreciation of the sufferings of St. Paul. Like him she had been imprisoned and harshly dealt with. With him she could say that she had been "In journeyings often, in perils of waters, in perils of robbers, in perils in the city, in perils in the wilderness, in perils in the sea; in weariness and painfulness, in watchings often, in hunger and thirst, in fastings often, in cold and nakedness."

One cannot gauge the effects of such a life. One can only admire, all must admire, in a spirit of humility, the heroism and devotion it portrays. Those of us whose associations with her lie only in our graduation from the same College and membership in the same profession, must place her high in our respect and admiration, for her life gave lustre to both her school and her calling, and so to us.

Winnipeg Medical Society

The regular meeting for January was held on Friday, the 16th, at the Winnipeg General Hospital. The attendance at this meeting seems to have been approximately twice the number usually present at the Winnipeg Medical Society Meetings, a fact which certainly attests the popularity of this type of program.

There were 48 demonstrations and displays located mostly in the Out-Patient's Department, 1st Floor, and the Operating Room of the hospital. It is not possible to list the different presentations let alone comment on them all. One was particularly impressed, however, by the presentations by the members of the Department of Medical Research. Certainly one has the feeling that many of the most recent biochemical and therapeutic techniques are readily available. I was also impressed with the presentations by members of the Orthopedics Department. There was a urological demonstration which was realistic down to the puddles on the floor. I believe also, that the Pathology Department's presentation entitled "Sudden Death," was considered one of the more interesting presentations.

General Practitioners

Valentine Party

The Glendale Country Club was the busiest and the happiest place in Winnipeg on February 14th. It was the first Valentine Dance known to have been held by the doctors in this city. Though it was sponsored by the General Practitioners Association of Manitoba, it was, nevertheless, for the entire profession.

Here new acquaintances were made and old ones renewed. It gave splendid opportunity for doctor's wives, who have not the same opportunity as the men, to see and meet each other again.

Following the liberal cocktail refreshments, 250 sat down in fine mood to a delicious dinner in fine surroundings. Everyone was happy and the place hummed with humor and conversation.

Dr. V. F. Bachynski of the G.P.A.M., was Master of Ceremonies. In the opening remarks he extended a cordial welcome to all the doctors, their wives and friends. He also expressed fitting acknowledgment to the Chairman of the Social Committee, Dr. A. J. Winestock, who devoted a great deal of time and effort to make the evening a success. Vote of thanks was paid to the management of the Glendale Country Club for extending the privileges of their premises to the doctors.

Dr. Roy Martin was called upon to propose the "Toast to the Ladies." Being in his usual fine mood he performed his duty with humorous remarks and anecdotes most appropriate for the occasion.

When Dr. K. Borthwick-Leslie stood up to respond to the toast, she took full advantage of the opportunity not to let any remarks made about the ladies go by without able retaliation. In her characteristic keen mood she did a fine job to retain the high status of her sex.

After the dinner more guests arrived. Then the air was filled with music and the spacious floor space was covered by the dancing feet.

During the intermission a talented floor show stirred up much laughter and roaring applause.

Everyone departed with the wish that this should become an annual social affair of the medical profession in Winnipeg.

Book Reviews

Second Annual Report on Stress. References to "Stress and the General Adaptation Syndrome" increase in number every year. Despite the elimination of papers concerned with borderline topics, last year's pertinent publications numbered over 4,000. This great amount of literature is gathered together and arranged in an ingenious and systematic manner.

After an introduction, which includes necessary explanatory data, there is a section devoted to "The Stress Concept in 1952." This includes a "Synopsis of the Stress Concept" and a discussion of the "Principal Objections Against the Stress Concept." In this the arguments of critics are set forth and answered.

There are about 300 pages of text in which the articles on each aspect, agent, organ, system and ailment are brought together. All papers referred to in the text are listed in a section of 173 pages. There is an atlas of over 60 photographs and microphotographs. There is a very complete index.

This "Annual Report," like its predecessor, has been prepared as a supplement to the original volume "Stress" which it brings up to date. The cross indexing is so comprehensive that in spite of the vastness of the literature—12,000 references in three years—it is very easy to find any one paper or all the papers on any topic, even a minor one.

Second Annual Report on Stress, by Hans Selye, M.D. (Prague), D.Sc., (McGill), F.R.S. (Canada), Professor and Director of the Institut de Medicine et de Chirurgie experimentales, Universite de Montreal; and Alexander Horava, M.D. (Lausanne), Research Associate and Librarian of the Institut. ACTH Inc. Medical Publishers, Montreal. Price $10.00.

Edinburgh Lectures on Medicine. The next best thing to listening to a lecturer is to read his lectures. In this volume are the lecture notes given to students of medicine in the University of Edinburgh.

In his preface Professor Davidson, of the Department of Medicine, tells how the book came to be published. It had been the practice for many years to give the students mimeographed notes so that an end might be put to the habit of students taking "extensive notes in long-hand, a practice which not only tends to ruin the students' hand writing, but which also limits their ability to concentrate on the subject under discussion."

The amount of labour and material which went into the preparation of these notes grew so great that the cost to each student was considerable. It was decided by Professor Davidson and his staff that they should amplify their notes and present them in printed form. The result is the book now before us.

Including the index it runs to 917 pages, comfortable both as to size of page and size of type. Excluded from it are special subjects such as infectious diseases, pediatrics and psychiatry Although there is no special chapter on psychiatry, "the psychological factor both in the causation and treatment of disease is frequently discussed."

It is written for the purpose of instructing students who will most of them go in for general practice. Therefore emphasis is laid on the common and usual. Each system and each disorder gets adequate consideration. The important and outstanding features are the ones stressed. There is little elaboration of detail—an advantage when one wants to get to the essence of the matter quickly.

There can be no question as to its authoritativeness or about its being up-to-date. Useful diagrams, tables, line drawings and photographs are in sufficient number to illustrate the text.

"The Principles and Practice of Medicine," a text book for Students and Doctors: By L. S. P. Davidson, B.A. Cantab., M.D., F.R.C.P. Ed., F.R.C.P. Lond., M.D. Olso, Physician to H.M. the Queen in Scotland, Professor of Medicine and Clinical Medicine, University of Edinburgh. Physician, Royal Infirmary, Edinburgh, and the Staff of the Department of Medicine and Associated Clinical Units. E. S. Livingstone Ltd., Edinburgh and London, 1952. Published in Canada by the Macmillan Company of Canada Ltd., Toronto. Price $6.25.

Lectures in Paediatrics

A course of lectures on practical aspects of Paediatric practice—some of clinical nature—are being arranged for Medical Practitioners during the winter months.

These will be given by local Paediatricians once weekly at the Pathology Lecture Theatre, Medical College, at 8 p.m., Monday.

For further particulars contact Dr. V. F. Bachynski, 92-5075 or 40-3825 (evenings).

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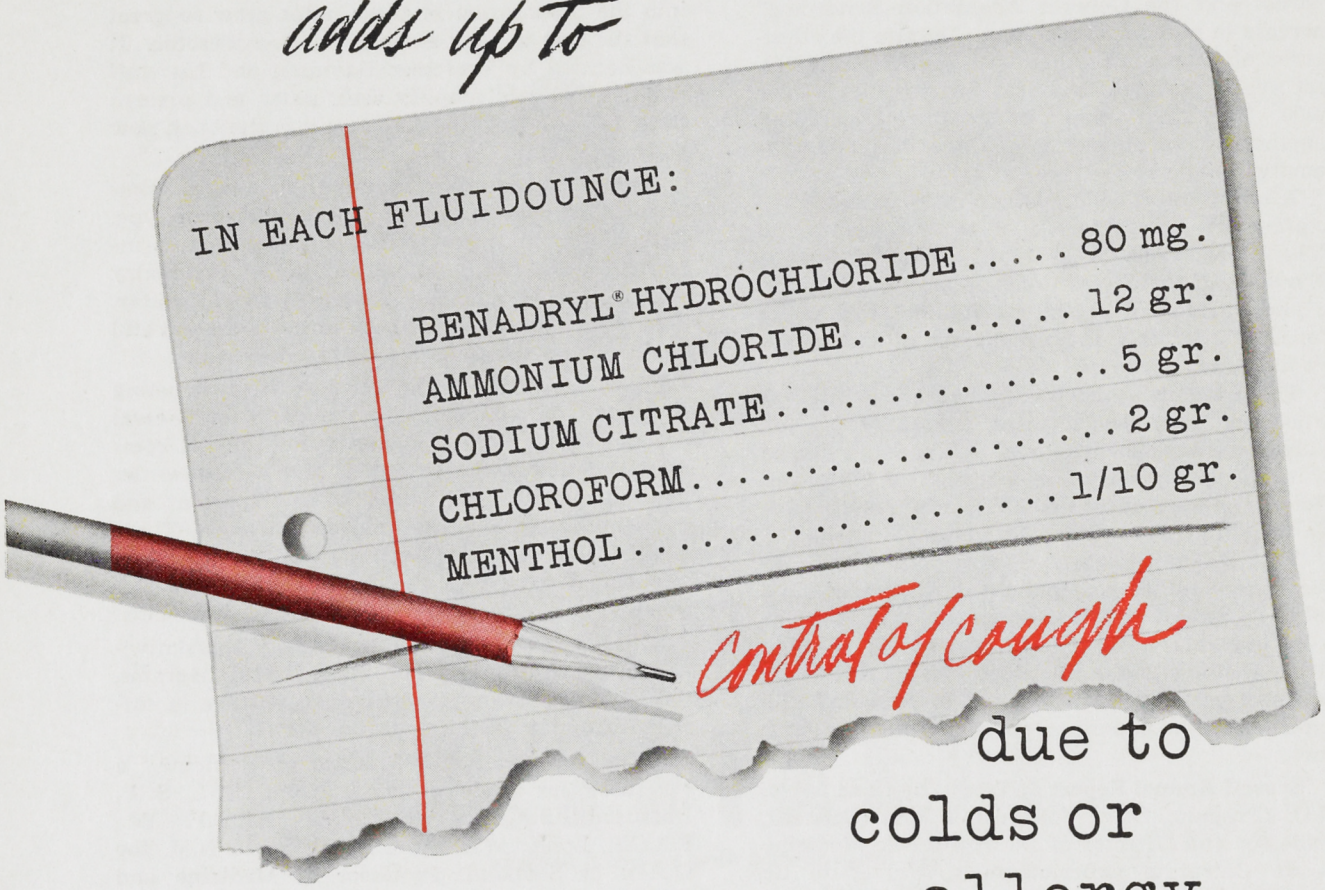

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Council Meeting (Cont.)

October 11, 1952

4. Reports of Standing Committees and Their Consideration

A. Executive Committee

Dr. C. B. Stewart advised there had been one meeting of the Executive Committee held since the May Council meeting, and that the minutes had been circulated to the members.

Change in Minutes, Executive Committee, September 23, 1952

The Registrar pointed out that in the minutes of the Executive Meeting held January 22, 1952, a motion was passed to reimburse the Manitoba Medical Association for stenographic assistance from October 1, 1951 - May 1, 1952; and in the minutes of the Executive Meeting held September 23, 1952, a motion was passed to reimburse the Manitoba Medical Association for stenographic assistance from June to September inclusive; leaving the month of May unaccounted for. The M.M.A. has been reimbursed for the month of May.

Motion: "THAT the motion passed at the Executive Committee held September 23, 1952, concerning reimbursing the Manitoba Medical Association, be changed to read 'for the months of May to September inclusive'." Carried.

Motion: "THAT the report of the Executive Committee as amended be accepted." Carried.

Business Arising from Minutes of Executive Committee, September 23, 1952

(a) Registrars' Meeting

The Registrar advised that the minutes of the Registrars' Meeting, held in Banff in June of this year, had been incorporated into the Executive Committee minutes and circulated to members of Council.

Under Standardization of Regulations for Issuing Enabling Certificates, D.6, it was agreed that this Council could not require a declaration of intention of Canadian Citizenship unless there was a complete change in policy. At the present time we issue Enabling Certificates to graduates of the United States, China, etc., who do not intend to practise in Canada.

(b) M.C.C. Candidates Required to Write Examinations in Manitoba

The Registrar presented a letter from the Registrar, Medical Council of Canada, in reply to his letter advising that this College was considering the requirement of a personal interview for all applicants, or the requirement that the examinations of the Medical Council of Canada be taken in Winnipeg. Dr. Argue advised that the C.P. & S. of Ontario interviews all applicants, but it is the privilege of any candidate who has enabling certificate to take his examination at whatever centre is most suitable to him, and the Medical Council of Canada makes no restrictions as to where a candidate may take his examination.

The Council agreed it would be wise to have an applicant for an Enabling Certificate sign a written agreement that he will write the Medical Council of Canada examinations in Winnipeg.

Motion: "THAT candidates for the Medical Council of Canada examinations, excluding candidates registered with this College as undergraduates, who request a regular Enabling Certificate through the College of Physicians and Surgeons of Manitoba, be required to undertake a written agreement that they will write their examinations in Winnipeg, and that the signature on the application form be attested by a notary public or commissioner of oaths." Carried.

(c) Community Chest and Council of Greater Vancouver, Re Narcotics

After study of the recommendations by the Community Chest and Council of Greater Vancouver, the Council agreed the matter should be given more serious consideration by a special committee.

Motion: "THAT Dr. Ed. Johnson be appointed Chairman of a committee which he shall name, to study the recommendations of the Community Chest and Council of Greater Vancouver, and report the findings to Council." Carried.

(d) General Medical Council of Great Britain, Re Interneship Requirement

The Registrar presented the communication from the General Medical Council of Great Britain advising that effective Jan. 1, 1953, one year's interneship would be required before registration on the British register. This was accepted as information only.

B. Registration Committee

1. Since the annual meeting of Council in October, 1951, the Registration Committee has met on eight occasions.

2. Twenty enabling certificates were granted. Certificate of registration was authorized in thirty-nine instances. Ten certificates of licence were granted and one was reinstated. There were twenty-nine deferments of applications for enabling certificates. Five applications for certificate of registration were deferred. One application for registration is pending and has neither been approved nor deferred because the applicant was a member of the Royal Canadian Air Force and had been posted abroad temporarily.

3. The Registrar's office and the Registration Committee continue to be heavily occupied with

a large number of foreign applications. The Committee now feels that it is able to handle these applications more efficiently because of accumulating experience. The great clerical burden thrust on the office of the College has made it necessary to recommend to Council that a documentation fee of $25.00 be charged all applicants other than those from our own school. A notice of motion was introduced to Council last May and will be dealt with at this meeting.

4. The Registrar and the Registration Committee have had special difficulty in handling the problem created by the issuance of an enabling certificate to a Persian doctor who subsequently failed completely in three trials of the Medical Council of Canada examinations. The College then withdrew the certificate and were influenced in doing so by the fact that the candidate had failed so completely on three occasions and had also been under considerable difficulty with the Federal authorities over his immigration status. This candidate has been working in a tuberculosis hospital in Ontario and now desires to write his examinations. It was the ruling of the Registrar that a new enabling certificate would be required. To obtain a certificate this candidate would now have to pass his Basic Sciences qualifications and would have to give evidence of a satisfactory interneship. These extra requirements, of course, make his personal problem greater and he maintains that his original enabling certificate should be his permanent right to take further examinations. He has embarrassed the College by taking lgeal action, to the extent of retaining legal advisors. This difficulty should not arise in the future because the new regulations of the Medical Council of Canada have removed any implication of permanence from the enabling certificate and specifically require the issuance of a new enabling certificate to candidates who have completely failed the examinations on two occasions.

5. The Registration Committee recommends to Council that foreign graduates desiring enabling certificates from this College be notified that they will be required to write the examinations of the Medical Council of Canada in Winnipeg. This is thought to be desirable because it would permit the candidate to be present in person instead of making all the negotiations by mail. Further, his oral examinations would be given by members of the University of Manitoba which would give the College a more personal evaluation of the candidate's standing. It is the opinion of the Committee that if Manitoba is used for the purpose of registration with the object of practising elsewhere in the world, it is not too much to require that the candidate visit Winnipeg and be examined here.

6. It has been the policy of the College to grant a temporary certificate of licence to graduate internes in the hospitals. Some of these internes have unwisely and without authority considered their temporary certificate as adequate to cover locum tenens. The Committee has instructed the Registrar to post notices in each hospital that such certificate of licence does not permit temporary practice as a locum tenens and that this matter might be important to the individual concerned if he became involved medico-legally.

7. Reciprocity with the General Medical Council of Great Britain has occasionally provided difficulties in interpretation. Doctors who are on the domestic list of the General Medical Council, if they have the necessary interneship and other basic requirements, are registered by reciprocity. Those who hold British qualification on the commonwealth and foreign lists are more difficult because the General Medical Council does not hold that our reciprocity agreement applies to them and it has been the policy of the College in the past to consider each applicant on merit. At present a graduate of the Polish School of Medicine, Edinburgh, has been accepted for appointment on the staff of the Hospital for Mental Diseases at Selkirk. He is prepared to write the examinations of the Medical Council of Canada and in the interval a temporary certificate of licence has been issued to him for a period of twelve months on the basis of documentation and the recommendation of the Superintendent of the above-mentioned hospital. During these twelve months he will be interviewed, his status reassessed and he will be requested to write the examinations of the Medical Council of Canada in the spring of 1953. This case is mentioned in some detail as an example of the nature of the problem of registrants of the various lists under the General Medical Council of Great Britain.

8. It is my opinion that the work of the Registration Committee will continue to be heavy for some years to come.

All of which is respectfully submitted.

C. H. A. Walton, M.D.,
Chairman.

Motion: "THAT the report of the Registration Committee be adopted." Carried.

C. Education Committee

No meeting.

D. Finance Committee

Dr. Williams advised there had been no meeting of the Finance Committee held since the May meeting of Council.

He suggested that the Notice of Motion concerning the documentation fee to be charged "before documents will be examined for eligibility" should be changed to read "required from all except Manitoba graduates and those who hold the Certificate of the Medical Council of Canada who apply for Enabling Certificates or Registra-

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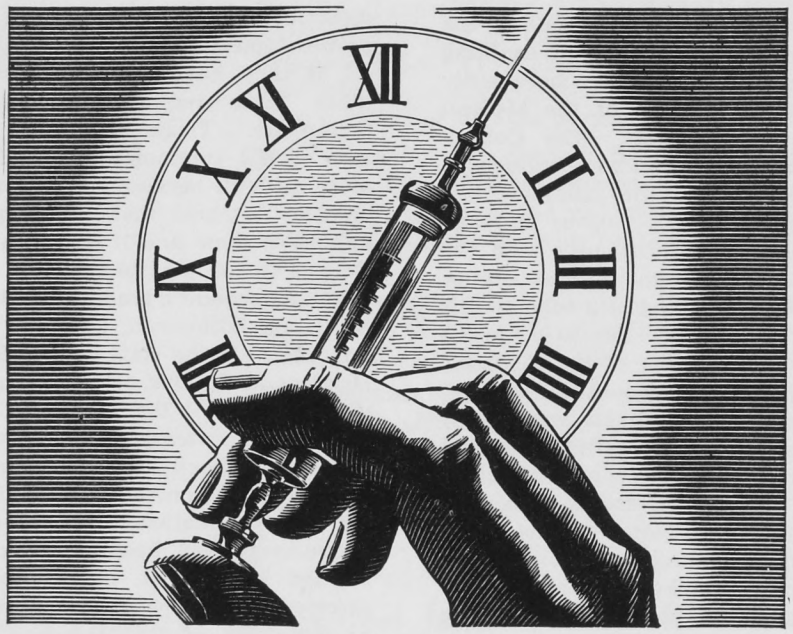

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tion," and that the motion be made retroactive to May 18, 1952.

He advised a communication had been received from the agent for the Apex Building, advising that the owner would be willing to accept less than the $100,000.00 which had been suggested. No action was taken on this matter.

Motion: "THAT the report of the Finance Committee be adopted." Carried.

E. Library Committee

Dr. Ed. Johnson presented the following statistics as prepared by Miss Ruth Monk, Medical Librarian.

Statistics, 1951-52

Contents of Library

1. BOOKS, BOUND and UNBOUND Serials (Periodicals): The approximate number of volumes in the library, exclusive of the duplicate files of serials:

1951-52	1950-51
18,446 volumes	17,889 volumes

Progress:
557 volumes, or an increase of 3.11% over 1950-51

2. SERIALS (Periodicals). Titles currently received:

	1951-52	1950-51
Titles	344	331
Duplicates	3	4
	347	335

Progress:
Increase of 12 titles or 3.58% over 1950-51

Volumes added to the Library by THE COLLEGE OF PHYSICIANS AND SURGEONS' grant —111 volumes.

This is a decrease of 30 volumes from last year's purchases on the above grant.

These 111 volumes comprise 31.98% of all purchases in 1951-52, and 25.46% of the total accessions.

Motion: "THAT the report of the Library Committee be adopted." Carried.

Borrowers — Registered Physicians

(a) Registered Physicians, Winnipeg and Suburbs

		Actual borrowers	% of registered city physicians
Medical Faculty	167	108	
Non-faculty	393	136	
Total registered city physicians	560	244	43.57%

Decrease in number of actual borrowers since 1950-51—16.
Total No. of items loaned to city physicians—3,578 or 40.4% of all loans in 1951-52.
This represents a decrease of 1,062 items or 22.8% since 1950-51.

(b) Registered Rural Physicians

		Actual borrowers	% of registered rural physicians
Total rural physicians	234	26	11.11%

Decrease in number of borrowers since 1950-51—6 or 18.75%.
Total number of items loaned to rural physicians—187.
This represents an increase of 23 items or 14% since 1950-51.

1. Registered urban physicians (Winnipeg and suburbs)

	Total Possible Borrowers	Actual Borrowers	% of Possible Borrowers	Increase in Borrowers over 1950-51	Total items loaned (Bks. & Jnls.)	Increase or Decrease from 1950-51	% Change from 1950-51
a. Faculty	167	108	64.67%	Inc. 18 or 20%			
b. Non-Faculty	393	136	34.60%	Dec. 34 or 20%			
	560	244	43.57%		3,578	Dec. 1,062	22.8%
2. Registered rural physicians	234	26	11.11%	Dec. 6 or 18%	187	Inc. 23	14%
Total Registered Man. physicians	794	270	34%	Dec. 22 or 7.50%	3,765	Dec. 1,039	21.6%

An increase of 25 in actual numbers of Registered Physicians, or 3.20% over 1950-51.
Note—Registered Manitoba physicians have borrowed 3,765 of the 8,843 or 42.57% of the items loaned in 1951-52.

October 4, 1952.

Re Grant to Medical Library Committee

A communication was read from the Chairman, Medical Library Committee, requesting the usual grant.

Motion: "THAT the College of Physicians and Surgeons of Manitoba grant to the Medical Library Committee, the sum of Seven Hundred and Fifty Dollars ($750.00) for the year 1952-53, to be paid from the Investment Trust Account." Carried.

F. Legislative Committee

The Registrar presented a complete report prepared by Dr. C. W. Wiebe concerning the changes in the Medical Act. The Council tendered a vote of thanks to Dr. Wiebe for his work in preparing these changes.

It was considered that the new Legislative Committee should take over the study of these recommendations, and that the Executive Committee be empowered to act, so that the amendments could be presented to the coming session of the Legislature.

Motion: "THAT the study of the changes in the Medical Act be referred to the new Legislative Committee, and that the Executive Committee be instructed to prepare the necessary amendments to the Act on the basis of recommendations of the Legislative Committee, to be presented before the next session of the Manitoba Legislature." Carried.

G. Taxing Committee

No meeting.

H. Discipline Committee.

No meeting.

5. Reports of Special Committees and Their Consideration

A. Representatives to the Manitoba Medical Association Executive

Dr. C. B. Stewart advised he had attended meetings of the Manitoba Medical Association Executive, but had nothing special to report.

Request for Grant for Extra Mural Postgraduate Work

A communication was read from the Manitoba Medical Association, requesting the usual grant for extra mural postgraduate work.

Motion: "THAT the College of Physicians and Surgeons of Manitoba grant to the Manitoba Medical Association, a sum up to Five Hundred Dollare ($500.00) for the season 1952-53, for extra mural postgraduate work, to be paid from the Investment Trust Account." Carried.

Request for Grant for Fee Assessment Committee, Workmen's Compensation Board

A communication was read from the Manitoba Medical Association, requesting the usual grant for payment of the Fee Assessment Committee, Workmen's Compensation Board. With revision of the Workmen's Compensation Board Fee Schedule, more meetings of this Committee may be anticipated.

Motion: "THAT the College of Physicians and Surgeons of Mantoba grant to the Manitoba Medican Association, for payment of the Fee Assessment Committee, Workmen's Compensation Board, for the season 1952-53, a sum at the same rate as members of the Council are paid for attending committee meetings." Carried.

B. Trustees of the Gordon Bell Memorial Fund

No further report.

C. Representatives to the Committee of Fifteen

No report.

D. Representative to the Committee of Selection in Medicine

The Committee met early in July at the University under the chairmanship of the President of the University. The applicants for entry to the course in Medicine were carefully screened and a sufficient number chosen. The successful students having fulfilled the requirements in the Pre-Medical course provided approximately 3/5 of the 70 students required. The balance were chosen from applicants who were graduates in Science and other faculties and who had fulfilled the requirements and had satisfactory academic standing.

In order to obtain a full class it was necessary to drop the average 2 or 3 points below the 65% which is usually considered the floor for admission. The veteran applicants are now pretty well taken care of from the last war and those from the present war have not yet qualified for admission so the glut of applicants is for a time passed. In any cases where there was doubt the background and activities of the applicant were enquired into.

The question of personal interview of applicants was gone into and well discussed. The committee concluded finally that:

(1) Inasmuch as the interview technique is subjective it would be difficult to defend if challenged;

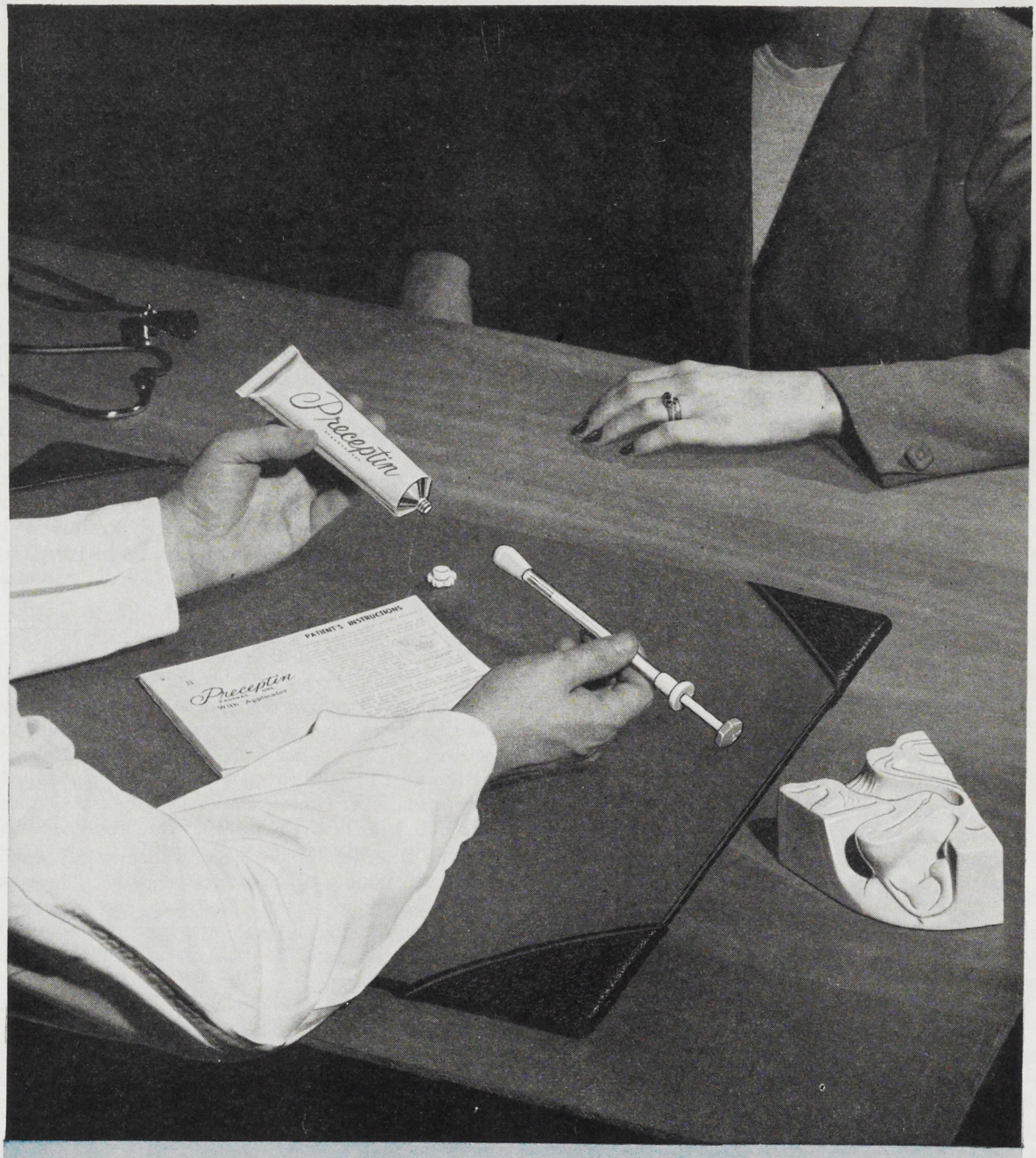
(2) There is no conclusive evidence that it can be classified as a sure test;

(3) It would be difficult to arrange because less than two-thirds of the number of applicants would likely be available for interview in Winnipeg.

It was therefore concluded that the personal interview would not be certain to give dependable results and would be most difficult to adhere to and that it would be wiser to accept a larger number of academically prepared students and weed out the least promising ones early in the Medical course.

Your representative has stressed the personal interview requirement but has to admit along with Dean Bell, Professor J. D. Adamson and Professor C. W. Burns that it is uncertain in its application and extremely difficult to carry out since many of the applicants are far from Winnipeg when their examination results are known and they then apply to enter Medicine.

The Committee continues to seek the best



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available applicants for entering the study of Medicine without bias or favor in any case.

Respectfully submitted,

T. H. Williams, M.D., C.M.

Motion: "THAT the report of the Representative to the Committee of Selection in Medicine be adopted." Carried.

E. Representatives to the Medical Council of Canada

Dr. C. E. Corrigan advised that he and Dr. C. H. A. Walton had attended the meeting of the Medical Council of Canada at Ottawa in September. One important item of business was the adoption of a resolution to implement the requirement of one year's interneship before registration under the Medical Council of Canada. A candidate can take his examination, but will not be registered until he has satisfactorily completed one year's interneship. Last year this College complained that there were not sufficient oral examiners since there were as many as 90 students wrote in the Spring. The Medical Council of Canada has accepted a recommendation of a duplicate slate of oral examiners for the Spring examination.

Dr. Walton advised that the word "permanent" had been dropped from the Enabling Certificate, and if a candidate fails twice he loses his Enabling Certificate.

Motion: "THAT the report of the Representatives to the Medical Council of Canada be adopted." Carried.

F. Representative to the University Senate

1. No matters of particular interest to this College have come up for consideration at the meetings of the Senate of the University.

2. As your representative on the Senate I continue to serve on the Senate Committee for the administration of the Basic Science Act. As usual, the Basic Science Committee has had a large number of applications for certification under the Act. There have been no major changes of policy since my last report. Again, I feel it important to record my opinion that the Basic Science Committee acts as a most useful and important screen of applicants to this College, for enabling certificates and licensure.

3. I have also acted as a member of the Senate Committee on Nursing Education. This school continues to carry on a rather precarious existence with very limited funds. I feel that it is making a very valuable contribution to post graduate nursing education in this province and it is hoped that it may continue to operate and that the ultimate goal of a degree course in nursing may finally be achieved.

4. Since the retirement of Dr. A. T. Mathers from the Senate a year ago, Dr. J. M. Lederman has been the Chairman of the Basic Science Committee.

All of which is respectfully submitted.

C. H. A. Walton, M.D.

(The Board of Governors of the University authorized the following changes in fees for a Certificate of Credit and for Basic Sciences examinations, effective September 18, 1952:

1. The fee for a certificate of credit issued to a candidate who is not a graduate in Medicine from the University of Manitoba will be $10.00. No fee for a certificate of credit will be charged an applicant who is a graduate in Medicine from the University of Manitoba.

2. Each candidate writing a Basic Science examination will pay an examination fee of $20.00 for each examination written).

Motion: "THAT the report of the Representative to the University Senate be adopted." Carried.

G. Representatives to the Cancer Institute

The Registrar explained that the President and Registrar of the C.P. & S. are ex-officio members of the Board of the Cancer Institute. At the Annual Convention of the Manitoba Medical Association it was reported that the agreement concerning the cancer diagnostic clinics has been operative for two years and should be reviewed. One other item was a verbal communication from Dr. R. F. Friesen, medical representative on the Cancer Institute, concerning the use of radium. The whole problem was dealt with some years ago and the question was who may use radium and who shall decide. The Medical Advisory Committee was not prepared to take on this assignment and the committee appointed was the President and Registrar, ex-officio members, and the Director who is a physicist. There have been few meetings of that committee and just recently Dr. Friesen wished to convene a meeting at the time of the M.M.A. Convention, but the gathering was postponed. The matter was discussed with Dr. Friesen and Dr. Purdie and the feeling was that it should be referred to Council.

Dr. Purdie stated there should be a referee board to decide who shall and who shall not use radium. It is outside the powers of this Council since we are a licensing body only.

Dr. Corrigan advised there was reason for concern. The Institute was involved in a very expensive law suit because they refused to allow a certain doctor to use radium, and is looking for someone to back them up.

Dr. Malyska said that doctors do not pay for radium from the Cancer Institute. A committee should be appointed to investigate the standards the Cancer Institute demand in order to obtain permission to use Manitoba Government-subsidized radium.

Dr. Macfarland questioned the power which the Executive Director of the Cancer Institute has in the appointment of medical personnel to a committee of this kind. Since he has been representing

the College he has had no reference brought to his attention concerning the appointment of personnel, or the appointment of Dr. Friesen to take the place of Dr. Macdonald on this committee of three.

Dr. Walton thought it would be a good thing to refer this to the Medical Advisoy Board for advice.

Motion: "THAT the report of the representatives to the Cancer Institute be adopted, and that the Registrar be instructed to take up the problem of radium lists with the Medical Advisory Committee of the Cancer Institute for direction." Carried.

H. Representatives to the Liaison Committee—M.M.A. & C.P. & S.

Dr. Johnson advised a meeting of the Liaison Committee had been held September 23rd, at which problems relating to the M.M.A. and C.P. & S. were dealt with, and from that meeting recommendations were made to the Executive Committee and were dealt with on the same day, and are included in the minutes.

Motion: "THAT the report of the representatives to the Liaison Committee—M.M.A. & C.P. & S. be adopted." Carried.

I. Representative to the Canadian Arthritis and Rheumatism Society—Manitoba Division

The Registrar advised he had attended all meetings, but had nothing to report.

J. Representatives to the Specialist Committee

1. The Committee has met on two occasions since it was appointed at the annual meeting in October, 1951.

2. The Committee consists of the following:

Representatives of Faculty of Medicine:

1. Dr. B. D. Best
2. Dr. Norman L. Elvin

Representatives of the Man. Med. Association:

1. Dr. F. G. Allison
2. Dr. M. R. MacCharles

Representatives to the C.P. & S.:

1. Dr. F. K. Purdie
2. Dr. C. H. A. Walton (Chairman)

Registrar, ex-officio, Dr. M. T. Macfarland

3. Thirty-nine applications for specialist registration have been received by the Registrar and have been granted under the provision of the by-law because of qualifications under the Royal Colleges of Canada. Eleven applications have been considered by the Committee from applicants who did not qualify automatically under the by-law. Of this number five were approved by the Committee for the Specialist Register and six were deferred for further action and study.

4. I would recommend that suitable notifications be again published in the Manitoba Medical Review drawing the Register to the attention of specialists in Manitoba.

5. The Committee on Specialist Registration requires direction from Council concerning special categories of specialist registration. These special categories are not included in the Royal College lists and yet might be acceptable categories of specialization within the meaning of our by-law. Examples presently under consideration are Industrial Medicine and Aviation Medicine. Does Council wish the Committee on Specialist Registration to make rules for each specific instance not otherwise covered?

All of which is respectfully submitted.

C. H. A. Walton, M.D., Chairman.

Motion: "THAT the report of the representatives to the Specialist Committee be adopted." Carried.

Motion: "THAT the notice concerning specialist registration be published in the Manitoba Medical Review on three occasions before January 1, 1954." Carried.

Motion: "THAT the Specialist Committee be given power to make decisions with regard to the eligibility of specialties for registration." Carried.

6. Election of Officers and Standing Committees

Officers

(a) President:

"THAT Dr. C. E. Corrigan be appointed President." Carried.

(b) Vice-President:

"THAT Dr. T. W. Shaw be appointed Vice-President." Carried.

(c) Registrar

"THAT Dr. M. T. Macfarland be appointed Registrar." Carried.

(d) Treasurer:

"THAT Dr. T. H. Williams be appointed Treasurer." Carried.

Nomination Committee to Strike Standing Committees

The President appointed Doctors C. H. A. Walton, W. J. Boyd and Wm. Malyska, as a Committee to Strike Standing Committees.

Dr. F. K. Purdie vacated the Chair, in favour of the newly elected President, Dr. C. E. Corrigan.

Standing Committees

(a) Registration Committee:

Dr. C. H. A. Walton, Chairman
Dr. F. H. Smith
Dr. W. J. Boyd

(b) Education Committee:

Dr. A. R. Birt, Chairman
Dr. A. L. Paine
Dr. W. J. Boyd

(c) Finance Committee:

Dr. T. H. Williams, Chairman
Dr. F. K. Purdie
Dr. B. Dyma

(d) Legislative Committee:

Dr. W. J. Boyd, Chairman
Dr. A. L. Paine
Dr. S. S. Toni
Dr. T. W. Shaw
Dr. A. R. Birt

(e) Discipline Committee:

Dr. Ed. Johnson, Chairman
Dr. Wm. Watt
Dr. T. W. Shaw
Dr. Wm. Malyska
Dr. A. P. Guttman

(f) Executive Committee:

Dr. C. B. Stewart, Chairman
Dr. G. H. Hamlin
Dr. Ed. Johnson
Dr. C. H. A. Walton
Dr. A. R. Birt

(g) Library Committee:

Dr. T. H. Williams

(h) Taxing Committee:

Dr. C. B. Stewart, Chairman
Dr. B. Dyma
Dr. P. Johnson

Motion: "THAT the appointment of standing Committees be accepted." Carried.

Election of Special Committees

(a) Representatives to the Manitoba Medical Association Executive

"THAT our representatives to the Manitoba Medical Association Executive be Dr. Ed. Johnson and Dr. C. B. Stewart." Carried.

(b) Representatives to the Committee of Fifteen

"THAT our representatives to the Committee of Fifteen be Dr. W. J. Boyd, Dr. F. K. Purdie and Dr. Ed. Johnson." Carried.

(c) Representative to the Committee of Selection in Medicine

"THAT our representative to the Committee of Selection in Medicine be Dr. T. H. Williams." Carried.

(d) Representatives to the Medical Council of Canada

"THAT our representatives to the Medical Council of Canada be Dr. C. E. Corrigan and Dr. C. H. A. Walton, for a four-year term." Carried.

(e) Representative to the University Senate

"THAT our representative to the University Senate be Dr. C. H. A. Walton as agreed at the May Council Meeting." Carried.

(f) Representatives to the Liaison Committee—M.M.A. & C.P. & S.

"THAT our representatives to the Liaison Committee—M.M.A. & C.P. & S. be Dr. C. B. Stewart, Dr. F. K. Purdie and Dr. Ed. Johnson." Carried.

Department of Health and Public Welfare

Comparisons Communicable Diseases — Manitoba (Whites and Indians)

DISEASES	1952 Jan. 1 to Jan. 24,'53	1952 Nov. 30 to Dec. 27,'52	1951 Jan. 1 to Jan. 26,'52	1951 Dec. 2 to Dec. 29,'51
Anterior Poliomyelitis	6	23	0	3
Chickenpox	176	233	138	190
Diphtheria	3	0	1	0
Diarrhoea and Enteritis, under 1 yr.	1	17	1	5
Diphtheria Carriers	0	0	0	0
Dysentery—Amoebic	0	0	0	0
Dysentery—Bacillary	0	4	0	2
Erysipelas	0	3	3	1
Encephalitis	0	0	0	0
Influenza	1	9	5	5
Measles	539	468	146	127
Measles—German	5	1	0	3
Meningococcal Meningitis	4	1	0	0
Mumps	128	102	151	165
Ophthalmia Neonatorum	0	0	0	0
Puerperal Fever	0	0	0	0
Scarlet Fever	40	47	67	82
Septic Sore Throat	0	2	1	3
Smallpox	0	0	0	0
Tetanus	0	0	0	0
Trachoma	0	0	0	0
Tuberculosis	15	53	27	0
Typhoid Fever	0	0	0	0
Typhoid Paratyphoid	0	0	0	0
Typhoid Carriers	0	0	0	0
Undulant Fever	0	0	0	0
Whooping Cough	8	10	31	58
Gonorrhoea	110	93	93	108
Syphilis	7	5	8	12
Infectious Jaundice	12	6	2	0
Actinomycosis	0	1	0	0

Four-Week Period January 1st to January 24th, 1953

DISEASES (White Cases Only) *Approximate population.	*798,000 Manitoba	*861,000 Saskatchewan	*3,825,000 Ontario	*2,952,000 Minnesota
Anterior Poliomyelitis	6	26	3	10
Chickenpox	176	136	3040	....
Diarrhoea and Enteritis, under 1 yr.	1	10	....	....
Diphtheria	3	....	....	....
Diphtheria Carriers	....	....	....	....
Dysentery—Amoebic	....	1	....	....
Dysentery—Bacillary	1	....	16	3
Encephalitis Epidemica	....	....	1	....
Erysipelas	....	5	4	....
Influenza	1	1	20	25
Infectious Jaundice	12	35	92	36
Malaria	....	....	....	1
Measles	539	531	3292	408
German Measles	5	19	93	....
Meningitis Meningococcus	4	3	5	6
Mumps	128	94	2266	....
Ophthal. Neonat.	....	....	....	....
Puerperal Fever	....	....	....	....
Scarlet Fever	40	199	370	128
Septic Sore Throat	....	63	3	7
Smallpox	....	....	....	....
Tetanus	....	....	....	....
Trachoma	....	....	....	....
Tularemia	....	....	....	3
Tuberculosis	15	24	72	17
Typhoid Fever	....	1	....	1
Typh. Para.-Typhoid	....	....	....	....
Typhoid Carrier	....	....	....	....
Undulant Fever	....	....	2	....
Whooping Cough	8	35	126	8
Gonorrhoea	110	....	185	....
Syphilis	7	....	54	....

***DEATHS FROM REPORTABLE DISEASES**

For the Month of January, 1953

Urban—Cancer, 57; Influenza, 1; Measles, 1; Pneumonia Lobar, 2; Pneumonia (other forms), 5; Poliomyelitis, 1; Tuberculosis, 1. Other deaths under 1 year, 21. Other deaths over 1 year, 228. Stillbirths, 11. Total, 260.

Rural—Cancer, 30; Influenza, 2; Measles, 2; Pneumonia, Lobar, 3; Pneumonia (other forms), 9; Poliomyelitis, 1; Diarrhoea and Enteritis (571.0) 3. Other deaths under 1 year, 16: Other deaths over 1 year, 134. Stillbirths, 14. Total, 164.

Indians—Other deaths under 1 year, 1. Other deaths over 1 year, 0. Stillbirths, 1. Total, 2.

♦

Poliomyelitis—The epidemic in 1952 was prolonged more than usual and we had several cases with onset in January, 1953, in fact twelve at date of writing (February 18th).

Chickenpox, Measles and Mumps are all epidemic at the start of the year.

Diphtheria—Three cases reported—all from the City of Winnipeg, a mother and son, and a two and a half year old boy unrelated to the other two.

Jaundice Infectious (or hepatitis) has been common in several parts of the province recently. It seems to be on the increase or we are in an epidemic cycle of this virus infection.

Detailmen's Directory

Representing Review Advertisers in this issue, whose names are not listed under a business address.

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